UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF WEST VIRGINIA

Biogen International GMBH
and Biogen MA, Inc.,

Plaintiffs,

vs. CIVIL ACTION NO.

1:17-cv-116

Mylan Pharmaceuticals, Inc.,

VOLUME III

Defendant.

- - -

TRANSCRIPT

of proceedings had in the bench trial of the above-styled action on February 7, 2020, before Honorable Irene M. Keeley, District Judge, at Clarksburg, West Virginia.

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INDEX TO WITNESSES

INDEX TO EXHIBITS

Friday Morning Session,

February 7, 2020, 9:00 a.m.

- - -

THE COURT: Good morning and welcome to a snowy day in West Virginia. We're ready to resume. I believe Dr. Greenberg; is that correct?

MS. BLOODWORTH: Yes, Your Honor. Thank you.

THE COURT: Mylan may call its next witness.

MS. BLOODWORTH: We call Dr. Greenberg, Your Honor, back to the stand. And, Your Honor, we have slimmed-down binders for the Court.

THE COURT: I like that, slimmed-down.

MS. BLOODWORTH: Except for the file history, which is one really large binder, but we're all going to use the same one.

THE COURT: Thank you. So that's a joint exhibit. Good.

BENJAMIN GREENBERG, **DEFENDANT'S WITNESS, SWORN**

DIRECT EXAMINATION (Continued)

BY MS. BLOODWORTH:

Q. Good morning, Doctor.

A. Good morning.

Q. Can you once again please state and spell your name for the record.

A. Benjamin Greenberg, B-E-N-J-A-M-I-N, G-R-E-E-N-B-E-R-G.

Q. Now, Dr. Greenberg earlier in the week, you offered opinions on obviousness, and today you're offering opinions about lack of written description of the '514 patent in the alternative, correct?

A. Yes.

Q. And that's how it was set up in your expert report?

A. Yes.

Q. And for the record, nothing has changed in your CV, DTX 1636, since Tuesday; is that correct?

A. Correct.

MS. BLOODWORTH: And, Your Honor, we incorporate Dr. Greenberg's background and education and experience into the record here today for the lack-of-written-description argument.

THE COURT: Yes.

Is there any objection?

MR. FELDSTEIN: No objection, Your Honor.

THE COURT: Thank you.

BY MS. BLOODWORTH:

Q. And, Dr. Greenberg, in creating or rendering or writing out your opinions here today, you reviewed the -- a declaration submitted to the patent office by Dr. Katherine Dawson; is that correct?

A. Yes.

Q. Okay. And if we could look at JTX 2173 at page 702,

paragraph 16, please.

And in Dr. Dawson's declaration in paragraph 16, she writes, "I conclude that a person of ordinary skill in the art would not have a reasonable expectation that a 480-milligram-day dose would provide statistically significant and clinically meaningful effectiveness for treating MS."

Did you rely on that statement in creating your alternative 112 opinions?

A. Yes.

Q. And if you were to credit Dr. Dawson's opinion as true, is there anything in the patent specification, in your opinion, that would convey to skilled artisans that the inventors had possession of a method of treating MS using 480 milligrams per day of DMF?

A. No.

Q. Have you chosen a claim to be representative of the three asserted independent claims?

A. Yes.

Q. Let's look at Representative Claim 1, please, which is on JTX 2000, which is the '514 patent, at page 28. And we also have it on the screen.

What elements are a part of Claim 1?

A. Essentially, there are three components to the claim.

It includes a method of treating multiple sclerosis. It includes the use of dimethyl fumarate, monomethyl fumarate, or

a combination thereof. And it uses 480 milligrams per day.

Q. And as you explained on Tuesday, the asserted claims of the '514 patent are -- it's your understanding are Claims 1 through 4, 6, 8 through 13, 15, and 16?

A. Yes.

Q. Okay. And also on Tuesday you provided a definition of a person of ordinary skill in the art, correct?

A. Yes.

Q. Okay. Let's remember what that is. If we look at Slide 2, what is your definition of a person of ordinary skill in the art for your opinions today?

A. As shown here, a person of ordinary skill in the art would be someone with at least a medical degree, at least three years of training in neurology, and at least three years of clinical experience treating multiple sclerosis.

Q. And did you review the specification of the '514 patent through the eyes of a skilled artisan from the time of the February 8, 2007, priority date?

A. Yes.

Q. And what was your opinion as to whether the patent has written description for the '514 patent asserted claims?

A. My opinion was that it does not.

Q. Now, if we could turn to Slide 4.

What standard did you use to analyze whether there is written description for the claims?

A. So the standard, as shown on this slide, Slide 4, was that the written description requirement is satisfied only if the specification of the patent conveys with reasonable clarity to a person of ordinary skill in the art that the inventor had possession of the claimed subject matter as of the filing date.
Q. And how did you approach determining whether there was written description of the patent claims?
A. So I started at the beginning of the patent with the specification and read through.
Q. Okay. And we're going to go over this specification in more detail. But at the outset are you aware that the patent application can disclose more than one invention?
A. Yes.
Q. And what is your understanding, as a skilled artisan, of what the '514 patent conveys?
A. So at a broad level the '514 patent conveys a screening method, looking at a variety of compounds, to determine whether or not they would impact biology that may be useful to patients with a variety of diseases.
Q. In creating and reviewing this -- in creating your opinions and reviewing this specification through the eyes of a skilled artisan, did you see any doses that you thought would be effective for treating MS?
A. So going through the specification, there are no specific doses identified as a therapeutically effective dose for

multiple sclerosis.

Q. And so let's go through the patent. If we could look at JTX 2000 at page 1, starting with the title.

What is the current title of the patent?

A. The current title of the patent is "Treatment for Multiple Sclerosis."

Q. And if we look at the abstract which is on the bottom right of page 1, as a skilled artisan, what do you take away from the abstract?

A. So at the high level, the very beginning of the specification, the abstract begins with "Provided are certain methods of screening, identifying, and evaluating neuroprotective compounds useful for treatment of neurological diseases such as multiple sclerosis," and it goes on to describe that the compounds may regulate a pathway that they refer to as the NRF2 pathway.

And then they discuss utilizing such compounds in the context of what had been screened in therapy for neurologic disease and outlined what the goals of those therapies would be, particularly slowing or reducing demyelination, axonal loss, or neuronal and oligodendrocyte death.

Q. And if we turn to Columns 1 and 2, what do Columns 1 and 2 -- excuse me -- what do Columns 1 and 2 teach a skilled artisan?

MR. FELDSTEIN: Your Honor, if I may, we've looked

carefully, and I don't believe that Dr. Greenberg offered any testimony regarding the disclosure of Column 2 of the '514 patent.

He discussed some parts of it but only a few parts of it. And he certainly, as I understand it from reading his report, had no opinions on anything in Column 2 of the '514 patent. So I believe the testimony that's being sought is beyond the scope of his report.

THE COURT: Would you like to respond to that, please?

MS. BLOODWORTH: Sure, Your Honor.

Dr. Greenberg testified that he read the entire patent specification, and there was no teachings in the specification that there was any written description. And then he went through and called out, you know, parts of it or whatever. But he made it very clear that he had read the entire specification and there was no teaching to a skilled artisan.

MR. FELDSTEIN: If all of his testimony is that he didn't find anything in Column 2, then I have no problem with that. But if he's going to testify substantively about what's in Column 2, I think that would be beyond the scope.

THE COURT: The scope of what? His report?

MR. FELDSTEIN: His expert report, yes, Your Honor.

THE COURT: The expert report, which I do not have,

would cover his opinions, the assumptions, if any, the bases. And one of the bases is "I read the patent"?

MS. BLOODWORTH: Yes, Your Honor.

THE COURT: Okay. Overruled.

MR. FELDSTEIN: Thank you, Your Honor.

BY MS. BLOODWORTH:

Q. Dr. Greenberg, looking at Columns 1 and 2, what do Columns 1 and 2 describe?

A. So the beginning of the specification under Column 1, after describing and indicating, "Provided are certain compounds for treating neurological diseases," it goes on to specify multiple sclerosis as a neurological disease and broadly defines what multiple sclerosis is and the population that is affected by multiple sclerosis.

After describing multiple sclerosis, it goes on to define a biologic pathway, specifically the NRF2 pathway, and how that has implications for what are called reactive oxygen species.

And in this context there is a description of the different diseases that can be affected or implicated by these reactive oxygen species and the NRF2 pathway relative to these conditions.

And after describing that pathway, it goes on to, at the bottom of Column 2, begin the outline of five methods that are within the patent.

Q. And do these five methods become the general sort of a

table of contents of the organization of the patent?
A. Yes.
Q. And, just briefly, what is Method 1 starting on the bottom of Column 2?
A. So Method 1 states a method of screening for at least one new candidate compound for treating a neurological disease.
Q. And Methods 2 and 3?
A. 2 and 3 go further in terms of evaluating the properties of at least one candidate. And in Method 3, it looks to compare different candidates with different compositions within the screening. They define it as bioequivalence.
Q. And what is Method 4 on the top of Column 3 of the patent?
A. On the top of Column 3, Method 4 is listed as "A method of treating a neurologic disease by administering to the subject in need thereof at least one compound that is partially structurally similar to DMF or MMF."
Q. And what is Method 5?
A. And then Method 5 essentially discusses combining two different therapies that may have an impact on the NRF2 pathway.
Q. And you were here for the opening arguments, correct?
A. Yes.
Q. And you heard that Method 4 and 5 were referred to as "the methods of treatment"?
A. Yes.

Q. Do you agree with that characterization?
A. So, broadly, Method 4 and 5 discuss methods of treating neurological diseases. Taken in the context of all five methods, it is cognitively in line with processing compounds that have been screened and then moving them into different scenarios. And so they talk to each other as they move through; but, broadly, it discusses treating.
Q. Okay. And how does the patent specification describe a neurological disease?
And if we could look at Column 3, lines 10 to 14, on the screen, you might be able to see it easier.
A. So at this portion of the specification, it describes "the neurologic disease is a neurodegenerative disease, such as" and it gives examples: ALS, which is known as Lou Gehrig's disease; Parkinson's disease; Alzheimer's; and Huntington's. And then it says that "In some embodiments, the neurological disease is multiple sclerosis or another demyelinating neurological disorder."
Q. And do you agree that a neurological disease would include MS?
A. Absolutely.
Q. Now, in your opinion, do any of the Methods 1 through 5 teach a skilled artisan about an effective treatment of MS with a 480-milligram dose of DMF?
A. They do not.

Q. So let's -- I think, following this, they start with some embodiments of Methods 1 through 3, beginning in Column 3 and going through Column 4.

What are these embodiments, generally?

A. So these embodiments flesh out what was outlined above, Methods 1 through 3, various different ways of screening compounds and looking at how those compounds would impact the NRF2 pathway.

And so it sets up a variety of different tests, including cell cultures and the like, to determine whether or not an agent of interest would affect this biologic pathway of interest.

Q. And let's turn to the embodiments of Method 4, which are on Column 4, starting at line 29 through 39.

What does the discussion of Method 4 in Column 4 teach a skilled artisan?

A. So at a high level, what it's discussing is providing a method of slowing or preventing neurodegeneration in a patient in need thereof by administering the compound in an amount and for a period of time sufficient to slow or prevent demyelination, axonal loss, neuronal death, e.g., by at least 30 percent relative to control.

And when discussing the compound, it's in reference to what was described above, "one neuroprotective compound having Formula I, II, III, or IV; e.g., a fumaric acid derivative

(e.g., DMF or MMF)."

Q. Okay. And so is that explaining to a skilled artisan -- or describing to a skilled artisan a method for treating -- an effective method for treating MS?

A. No.

Q. And if we turn to the embodiments of Method 5 at the bottom, Column 4, starting around line 39, what is the Method 5 embodiments here teaching?

A. So Method 5 fleshes out what had been described at the outset of this notion of combining different agents. And it's very specific to the notion of taking one agent that upregulates the NRF2 pathway, taking a second agent that doesn't have an impact on this pathway, and then putting them together to look at them in combination relative to a treatment of different neurological conditions.

Q. And then when you look through the specification again, it sort of goes back to Methods 1 and 3, starting at Column 6 through Column 8, and relates once again to the screening. Is that what's -- what's described on columns around 6 through 8?

A. Yes.

Q. So I'd like to turn to Method 4 on Column 8, lines 35 to 53.

And again, Dr. Greenberg, what's being conveyed in Method 4 on Column 8 to a skilled artisan?

A. So this is the third pass, if you will, at fleshing out

Method 4. The first was the high-level statement. The second was the embodiments we've discussed.

And now, in Method 4 on Column 8, it discusses methods of treating a neurologic disease by administering to the subject at least one compound that is at least partially structurally similar to DMF or MMF.

And it goes on to indicate that you would "administer to the mammal a therapeutically effective amount of at least one neuroprotective compound which has," and it outlines the formulas. And then it repeats the notion of slowing neurodegeneration, specifically talking about demyelination, axonal loss, and/or neuronal death.

And at the end sets up goals of that slowing of 30, 50, 100 percent or higher and talks about periods of time that range from 5 to 200 weeks or more.

Q. Does Method 4 describe an effective method for treating MS?

A. No.

Q. Why not?

A. So specifically in here is not any identification of a therapeutically effective amount. It is not indicating that you would give it in multiple sclerosis. It's setting up a hope.

It's setting up a notion of how you would screen agents, as I read this, looking at these marks of 30, 50, 100 percent

over time, what you would want to see, but it doesn't define a dose as therapeutically effective for multiple sclerosis.

Q. And at the bottom of Column 8 into the top of 9, there's another embodiment about Method 5, correct?

A. Yes.

Q. Okay. And then, following that, Columns 9 and 10, what do those lay out to the skilled artisan?

A. So this lays out the organic chemistry of the different reactions that could be used to create a compound library, if you will, a set of what had been referred to in the patent as compounds that are partially similar to DMF or MMF, and presumably this is the library that could be screened through the methods of the patent.

Q. If we can move forward to Column 16, please, and lines 18 through 34.

Now, this section here is referring to MS, correct?

A. Yes.

Q. And what is it teaching the skilled artisan?

A. So it's talking about the neurologic diseases in Methods 1 through 5 and gives examples -- ALS, Parkinson's, Alzheimer's, Huntington's -- and also includes -- goes on to define multiple sclerosis or other demyelinating diseases of the central or peripheral nervous system. And it does describe the different forms of multiple sclerosis, what are known as relapsing-remitting multiple sclerosis, secondary progressive

MS, and primary progressive MS.

Q. So with this paragraph wouldn't a skilled artisan understand that this patent was teaching you an effective dose for treating MS?

A. No.

Q. Why not?

A. So this paragraph and -- on its own and even with what we've reviewed in the specification thus far, doesn't describe a therapeutic effective dose to impact multiple sclerosis or any of the diseases that have been listed here.

Q. And we're not going to go through today every word of the patent specification, but to the extent, if we don't go over a reference to MS or to -- a reference related to MS, would any of those disclosures teach a therapeutic effective dose of 480 milligram?

A. They do not.

Q. Okay. So let's, then, turn to the examples.

Did you consider the examples in the specifications in arriving at your opinions?

A. I did.

Q. And what is your opinion of whether the examples provide written description sufficiently to support a therapeutically effective dose of about 480 milligrams a day of DMF?

A. My opinion is they do not.

Q. Okay. Why not, generally?

A. So, generally speaking, these examples are very much in line with the notion of screening compounds. They set up a variety of different paradigms to screen compounds to look at whether or not they would activate the NRF2 pathway But at a high level, none of the examples are screening compounds relative to a therapeutically effective dose for multiple sclerosis.

Q. Let's turn to Example 1, please, on page 24 at Column 19. It's the very bottom of 19. It actually goes over to Column 20, the top there.

What is Example 1?

A. So Example 1 again fits into this notion of screening. It starts with using a human colon carcinoma cell line called the DLD-1 cells and treating them with various concentrations of DMF or MMF for 16 hours and then taking those cells and looking at protein expression, what's referred to as a Western blot analysis, where you take the cells and you look to see if certain protein levels are changing. And they describe the parameters for testing that change of the NRF2 pathway.

Q. And around line 11 or 12 of Column 20, it references Figure 1.

A. Yes.

Q. What is Figure 1?

A. So Figure 1 is the results of this screening method. And they indicate that it demonstrated that DMF and MMF in

micromolar concentrations as listed on the slide, ranging from 5 to 50 micromolar concentrations, activated the NRF2 pathway.

Q. And looking at Example 2, beginning on Column 20 around line 16, what is Example 2?

A. So Example 2 is another way that a scientist could address the same question but with different parameters to the testing. It's screening the same cells, these cancer cells, grown in certain conditions and then exposed to DMF, in this instance, 30 micromolars of DMF for 40 hours.

And then what they did is affect what proteins would be available within the cell for an agent to bind to. And they're teasing out the pathway of the NRF2 pathway and proposing a screening mechanism to determine how a new compound would interact with this pathway.

Q. And approximately around line 52, Column 20, it references Figure 2.

A. Yes.

Q. What is Figure 2?

A. So, again, this is a Western blot. It's looking at proteins. And it indicated that, when you put DMF into cell lines to upregulate this protein, the NQO1 protein, that it required the NRF2 protein. And so if you -- when we're looking at proteins and they talk to one another in a cell, this is a method to screen for compounds to determine at which point in that communication pathway would they be talking to each other.

So it's screening in a more -- in a different way for that interaction.

Q. And do either Examples 1 or 2 or their respective figures describe a therapeutically effective dose of 480 milligrams a day of DMF?

A. No.

Q. Why not?

A. So, first off, the cells that are used in Examples 1 and 2 are a carcinoma cell line that have nothing to do with neurons or myelin or axons or oligodendrocytes or demyelination. And so the construct that's being proposed here, a skilled artisan would not read anything relative to multiple sclerosis in terms of the construct.

Secondly, the micromolar concentrations that these cells are being exposed to have no anchor point relative to any dosing. And so there's no way for a skilled artisan to go from this artificial construct about cancer to dosing relative to multiple sclerosis.

And, finally, there's no definition of a notion of what therapeutic efficacy is relative to the results that are being presented here.

So a skilled artisan reads this as a method for screening new compounds relative to the NRF2 pathway, but it doesn't tell me anything about multiple sclerosis or therapeutically effective doses for multiple sclerosis.

Q. So let's turn to the last example, which is Example 3. And I believe it's on page 24, Column 20. It begins at the bottom of Column 20, around line 60, and I think it then continues on to Columns 21 and 22.

What is Example 3?

A. So Example 3, which is the last of the examples in the specification, provides another mechanism for screening for NRF2 pathway activation. In this example, instead of doing the analysis in cell culture, the analysis was done in mice, referred to as EAE mice.

Q. And are there figures referenced in Example 3?

A. There are.

Q. If we turn -- they're referenced, I believe, around Column 22 around lines 12; but if we can look at Figure 3 first, what is Figure 3?

A. So Figure 3 is a histologic slide from the nervous system, from the spinal cord, of one of these EAE mice after exposure to different dosages of DMF.

Q. And let's look at Figure 4. What is Figure 4?

A. Figure 4 is looking -- taking data from these histologic slides and doing an analysis looking at upregulation of NRF2 in the spinal cord relative to different dosages of DMF and MMF.

Q. And you mentioned EAE. Isn't EAE a mouse model for MS?

A. It is.

Q. Just generally, what is EAE?

A. So EAE is an acronym that stands for experimental autoimmune encephalomyelitis. And, essentially, we induce a mouse's immune system to attack the brain and spinal cord.

So in this animal model of multiple sclerosis, we can track the clinical events and the pathologic events that happen in MS. So the mouse will develop weakness of their tail and weakness of their hind limbs. And when we look at tissue under the microscope, we can see the immune system invading the nervous system, and we can see the hallmarks of demyelination and axonal loss.

Q. In your opinion, does Example 3, including Figures 3 and 4, teach a skilled artisan about an effective treatment for MS?

A. No.

Q. We just talked about the EAE model being used in Example 3 and results in Figures 3 and 4. So, because they were EAE, the model, and they were EAE mice, doesn't this experiment relate to treatment of MS?

A. No.

Q. Why not?

A. So in order to relate -- in order for a skilled artisan to relate this to multiple sclerosis, it isn't just picking the EAE model; it's what analysis you do and what you present.

So there's no clinical scoring of the mice presented. There's no pathology of demyelination. There's no pathology of

axon loss. There's no measuring of the immune system's impact on the nervous system. All there is is taking the mouse and showing that the NRF2 pathway could change.

So, in a sense, it's screening for compounds that change the NRF2 pathway in this model, but that's different than the model showing a therapeutically effective dose.

Q. So is there anything in Example 3 or Figures 3 and 4 that teach a skilled artisan about an effective dose for treating MS using DMF?

A. No.

Q. So, in your opinion, would a skilled artisan find anything in these examples that is related to an effective dose for treating MS?

A. No.

Q. So we've gone through the examples in the figures. But doesn't the specification provide guidance for skilled artisans on how to determine a therapeutically effective dose?

A. So the specification does, in broad terms, talk about how skilled artisans routinely go about determining doses.

Q. And where does it do that?

A. So beginning in Column 17 and going through Column 18.

Q. So, in your opinion, what about dosing does -- do Column 17 to the top of Column 18 teach a skilled artisan?

A. So the end of Column 17 and the top of 18 are talking about general practices when a skilled artisan would pick a

dose. And it refers to the notion of determining the LD50 and ED50 and then using this information to determine how you would dose an individual with a condition.

And then it goes on to discuss also a method looking at something called the IC50 to pick levels of dosing individuals that you want to expose them to.

Q. What is LD50?

A. So LD50 is the dose lethal to 50 percent of the population. So, when finding -- when working with compounds and we're screening them and trying to determine if they might be therapeutically effective, once we have compounds of interest, we have to determine could a human tolerate the agent? And the LD50 is the dose at which we would kill half the population. So it gives us a pretty clear boundary and a sign to stay away from that level at all costs.

Q. And what is an ED50?

A. So the ED50 is the other end of the spectrum. It's looking for the therapeutically effective dose relative to 50 percent of the population. So it gives you the sense at what dose would you really start having a meaningful benefit to the population you're treating to target.

Q. And IC50, what is that?

A. So the IC50 is taking an animal model and looking to achieve circulating plasma concentrations. And to do this, you can estimate from cell cultures.

So if you take certain cell cultures, you can then take the data to an animal, but then you have to take the animal and go into the LD50 and ED50.

So this part of the specification is talking broadly about the routine approaches to dose-finding at a high level.

Q. Would any of this information be able to be combined with Examples 1 and 2 by the skilled artisan to teach an effective dose?

A. No.

Q. Why not?

A. Because Examples 1 and 2 don't define therapeutic efficacy. They aren't relative to multiple sclerosis. They're in a cancer cell. And there's no correlation between the micromolar concentrations that are designed there and any dosing regimens.

Q. Are Examples 1 and 2 in vitro experiments?

A. They are.

Q. What does that mean?

A. It means outside the body, outside a living organism, any mammal.

Q. And Example 3 is an in vivo example?

A. It is.

Q. So could you combine the teachings in Column 17 and 18 with Example 3 teachings to come up with an effective dose?

A. You can't.

Q. Why not?
A. Because what's lacking is any correlation between the micromolar concentrations and the effect on the cells, what's given to the mice. And, ultimately, none of the examples define therapeutic efficacy.

The examples define activation of an NRF2 pathway, but therapeutic efficacy, clinical efficacy to mouse or a human relative to preservation of myelin, axons, or prevention of symptoms isn't defined or explored in any of the three examples.

Q. So turning just back to Columns 17 and 18, is there any guidance disclosed -- is there any information disclosed to a skilled artisan about specific compounds that could be used to effectively treat MS?
A. No.
Q. And if we could go lower on Column 18, starting at line 14 to 33, what does this paragraph in Table 2 describe?
A. So this paragraph picks up where the others left off, where you have a dose that you're interested in, you've defined your LD50 and your ED50, and you say "I have dose X that I want to explore that I've looked at in the mouse" and it goes on to give other animals that we could look at. And it gives general guidance on how to extrapolate that dose in an animal, do a calculation, and have a guesstimate of how to get to a human dose.

Q. So what does, if anything, this -- the Table 2 in the paragraph, starting at line 14 on Column 18, teach the skilled artisan about a therapeutically effective dose for MS?
A. It doesn't.
Q. And, again, is Table 2 tied to any specific compounds?
A. It is not.
Q. Can any of the in vitro or in vivo data from either Examples 1 through 3 or Columns -- the information we've gone over in Columns 17 and 18 so far be used to extrapolate a therapeutically effective dose when the skilled artisan is reading the whole specification?
A. No.
Q. Why not?
A. Because the specification thus far, including the examples, has never shown therapeutic efficacy in multiple sclerosis, hasn't shown therapeutic efficacy in any neurologic disorder. Thus far, the specification has been discussing screening methods, ways to identify compounds that can alter the NRF2 pathway. And that's very different than anything relative to a dose -- a therapeutically effective dose to treat a specific disease.
Q. Now, doesn't Column 18, starting at lines 41 through 50, list doses that can be used to treat human patients?
A. Yes.
Q. And what is this discussing here?

A. So in Column 18, as shown on the screen, it talks about dosages -- in some embodiments, the dosage of such compounds lies within a range of circulating concentrations. And it goes on to say, "Generally, a therapeutically effective dose -- amount" -- excuse me -- "may vary with the subject's age, condition, and sex as well as the severity of the medical condition in the subject. Examples of acceptable dosages for the compounds are" -- and then it lists a series of different weight-based dosing regimens, the broadest of which is 1 microgram per kilogram, going to 25 milligrams per kilogram.

Q. Do you generally know what that range would be?

A. So for a human, if we take the average of 60 kilograms -- and I wish I was the average human -- it would range from .06 milligrams to 3,000 milligrams.

Q. And does this progressively narrowing range of doses describe to a skilled artisan a therapeutically effective dose for MS?

A. No. In this paragraph it says "The appropriate therapeutically effective dose can be selected by a treating clinician in some embodiments," and then lists narrowing ranges going from 1 microgram per kilo to 20 milligrams per kilo and then all the way down in its smallest range to 100 micrograms to 1 milligram per kilogram.

And this refers to treating clinicians picking within these ranges. It doesn't give any specificity as to what a

therapeutically effective dose would be and doesn't tie it to any particular condition.

Q. So it's not specific to MS?

A. No.

Q. And does this paragraph refer to DMF or MMF specifically?

A. No.

Q. So if we look at the next paragraph in Column 18, lines 52 through 54, those discuss DMF or MMF, right?

A. Yes.

Q. So -- and then, if we can look at the whole paragraph beginning on line 52 at Column 18, what is your opinion on whether the range of 1 milligram per kilogram to 50 milligrams per kilogram discloses -- whether that discloses an effective dose for treating MS?

A. So my opinion is it does not.

Q. What is that range generally?

A. So that range, when talking about one milligram per kilogram, which would be for an average human 60 milligrams, goes up all the way to 3,000 milligrams is a broad range, and it's basically saying DMF or MMF as an agent, when used to treat conditions, the effective range will be broadly between these two lines.

Q. And then starting at line 54, though, it starts with the words "Effective doses will also vary, as recognized by those skilled in the art."

Do you see that?
A. Yes.
Q. And what does this sentence mean to you?
A. So what it would mean to myself reading the specification is there's a recognition between these broad ranges that, depending on a variety of different factors -- and it lists here route of administration, excipient usage, possibility of co-usage with other therapeutic treatments, including use of other therapeutic agents.
And so it's telling me that we're entering a discussion of therapies where there's a lot of variance based on a lot of different covariants, including possible combination.
Q. And I asked the question what it meant to you. Were you speaking as a skilled artisan?
A. Yes.
Q. Sorry for the lack of clarity there.
So what is allometric scaling?
A. So allometric scaling is where we alter the dose based on a person's size, based on their weight or body surface area.
Q. And is that something that a skilled artisan is familiar with?
A. It is.
Q. And how would that impact the skilled artisan's reading of Columns 17 and 18?
A. So when reading through in Columns 17 and 18 and

specifically the paragraphs we're talking about, it tells the skilled artisan that, based on a variety of covariants, many of which have been listed here, a skilled artisan would pick multiple potential different dosages depending on size of the patient relative to allometric dosing or other variables that are being described here.

Q. And turning in Column 18, lines 58 through 62, and is the sentence that starts "For example, an effective dose of DMF or MMF" -- I believe that's a typo -- "MMF to be administered to a subject orally can be from about" -- and it lists a series of ranges.

Do you see that sentence?

A. I do.

Q. Does this sentence describe, for a skilled artisan, an effective dose of DMF to treat MS?

A. No.

Q. Why not?

A. So it starts off with "for example." It's pivoting from the prior sentence about this notion of effective doses varying on all sorts of different features, and then it goes on as above to give these broad ranges.

It starts with .1 gram to 1 gram, which is the equivalent of 1,000 milligrams -- excuse me -- 100 milligrams to 1,000 milligrams and then goes down subsequently to narrower and narrower doses. 200 milligrams to 800 milligrams a day, and

then, e.g., from about 240 to about 720 milligrams per day or from about 480 milligrams to about 720 milligrams a day or about 720 milligrams per day.

And so it leaves it as the prior two different discussions of dosing regimens in these broad goalposts and doesn't anchor to a therapeutically effective dose for multiple sclerosis.

Q. Is it discussing multiple sclerosis in this paragraph?

A. No.

Q. Could it be another neurological disease?

A. Yes.

Q. Would the skilled artisan know that it was speaking about MS?

A. No, not specifically. Given the whole specification, which has been screening for compounds for neurodegeneration, screening for compounds that alter the NRF2 pathway, the skilled artisan, getting to this point, recognizes that there are a variety of doses that could be used in a variety of situations, not just based on the condition but based on the person or their size and, in this instance, the notion of combining with another agent.

And so a skilled artisan would read this as there are lots of different approaches depending on specific situations, but this paragraph doesn't tie a dose to one of those specific situations as being therapeutically effective.

Q. Focusing on the part that says "from about 0.1 gram to

1 gram per day and to about 480 milligrams to about 170" -- excuse me -- "720 milligrams per day," do those all include 480 milligrams per day?

A. Yes.

Q. So why doesn't that teach a skilled artisan that the claimed therapeutic effective treatment for MS using 480 milligram of DMF would work?

A. So within this specification, going through these different ranges and taking just this, if you wanted to be restrictive, or the whole specification, if you wanted to view broadly, at no point do any of those doses get tied to therapeutic efficacy, 240, 480.

The narrowing of ranges here, there's no -- a skilled artisan wouldn't read this and have any knowledge that one particular dose relative to being therapeutically effective dose for MS existed as an entity. These are broad ranges.

Q. Is there any -- from your review of the patent specification, is there any clinical data in the patent?

A. No.

Q. Is there any prophetic examples about clinical data in the patent?

A. No.

Q. And you were here yesterday for Dr. Lukashev's deposition testimony, correct?

A. Yes.

Q. Was there anything in Dr. Lukashev's testimony that you heard that was inconsistent with your opinions?
A. No.
Q. And during the drafting of your expert report, you reviewed deposition transcripts of Dr. Gilmore O'Neill, correct?
A. Yes.
Q. And in your review of those deposition transcripts, was there anything that you read that was inconsistent with your opinions?
A. No.
Q. So, Dr. Greenberg, we've gone over the specification. Is there any disclosure in the patent specification that conveys with reasonable clarity that the inventors of the '514 patent had possession of an effective dose of 480 milligrams per day of DMF to treat MS as of the priority date?
A. No.
Q. And why not?
A. Because, reading through this screening patent, these methods to look for compounds that may be helpful to diseases, including multiple sclerosis, screening agents that may alter the NRF2 pathway, and examples that fit into this notion of screening compounds for impact on NRF2 pathway without any tying of a specific dose to a clinical benefit, a therapeutically efficacious dose in MS or even an animal model

of MS or a cell model of MS, I don't see why I would read the claim and assume anything in this specification would tell me they had that claim of 480 milligrams being a therapeutically effective dose of DMF or MMF for multiple sclerosis.

Q. And now, again, your opinions here today are on the -- under the assumption that Dr. Dawson's, for example, statements that the person of skill in the art would not have a reasonable expectation that the 480-milligram would provide statistically significant and clinically meaningful effectiveness for treating MS; is that correct?

A. Correct.

MS. BLOODWORTH: Thank you, Dr. Greenberg. I have no further questions.

THE COURT: All right. Thank you. You may cross-examine.

MR. FELDSTEIN: Thank you, Your Honor. We have binders to hand up.

CROSS-EXAMINATION

MR. FELDSTEIN: May I begin, Your Honor?

THE COURT: Yes, certainly.

BY MR. FELDSTEIN:

Q. Thank you. Good morning, Dr. Greenberg. How are you?

A. I'm well. Thank you.

Q. When you come in reading the '514 patent, you don't come in with no knowledge, correct? You come in with the knowledge

of the person of ordinary skill?
A. Correct.
Q. The person of ordinary skill coming to the '514 patent would have known that 720 milligrams per day was an effective treatment for multiple sclerosis, correct?
A. Yes.
Q. And so the person of ordinary skill didn't need to be convinced prior to the '514 patent that DMF was, at least some dose, therapeutically effective for treating multiple sclerosis, correct?
A. Yes.
Q. And the person of ordinary skill, the level of -- they're very high level, correct?
A. I think we've defined person of ordinary skill based on the definition, three years of education -- excuse me -- three years of neurology and experience in multiple sclerosis. If that's high level, yes.
Q. You'd agree that a person of ordinary skill has a considerable level of skill and experience?
A. Again, I just look at this through the lens of the definition we used, but I view three years as considerable experience.
Q. Considerable level of skill and experience, correct?
A. Yes.
Q. And the person of ordinary skill doesn't need proof to the

level that a regulatory agency would need, correct?
A. Correct.
Q. And coming into the '514 patent, you and a person of ordinary skill would see no reason why 480 milligrams of DMF would not be an effective dose for treating multiple sclerosis, correct?
A. So -- can you repeat the question? I'm sorry. There was a "not" in there.
Q. In all your work in preparing your opinions and everything that went into it, did you ever come across anything that would teach you that 480 milligrams would not work?
A. I did not come across studies where 480 milligrams had failed, if that's what you're asking.
Q. Okay. Let me bring up the trial testimony from day one, please. It should be in your binder, and I'm going to turn to page 185 and lines 21 through 24.

So you'd been discussing multiple sclerosis, and you were asked, "In all your work in preparing your opinions and everything that went into it, did you ever come across anything that would teach you that 480 milligrams would not work?"

And your answer was "I'm not aware of anything that would say that."

Correct?
A. Correct.

THE COURT: Just because I don't want to get into too

much of this this morning for delay purposes, I didn't understand his answer, that no studies of 480 milligrams would fail, to be inconsistent with the question you asked him or the impeachment you just went through.

So what was the purpose of the impeachment?

MR. FELDSTEIN: I think the answer was more equivocal than what he testified to before.

THE COURT: Let me stop you for a second. I didn't see that. If we're going to do this all morning, I want to stop it now.

MR. FELDSTEIN: We're not going to do it all morning, Your Honor. I apologize.

THE COURT: Just want to make sure about that.

BY MR. FELDSTEIN:

Q. So I'd like to look at the prosecution history that you were looking at, Dr. Greenberg. And I'd like to turn, if we can, to JTX 2173, page 60.

A. I'm sorry. Could you repeat the JTX.

Q. It's the large binder that your counsel had given you of the file history. It's JTX 2173, page 60.

A. Yes.

Q. And you had reviewed this when you had reviewed the prosecution history, correct?

A. Yes.

Q. And this is a preliminary amendment where the claims that

are now in the patent were added, correct?
A. Yes.
Q. And if we go to page 63 -- 62 to 63, there's Claim 32 that's split across the page, pages 62 to 63.
A. Yes.
Q. And if you can switch in our binder -- or we can just put up on the screen to the patent, JTX 2000 -- I want to confirm if we put it up on the screen, this is the same claim as Claim 15 in the issued patent, correct?
So we'll put it up on the screen or you can look at it. I'm comparing Claim 32 from JTX 2173, page 62 to 63, with Claim 15 in Column 30 of the '514 patent, JTX 2000.
A. Yes.
Q. Okay. Now, if we continue to go forward in the amendment, if we turn to JTX 2173, page 64, there's a section "Summary of the Claimed Subject Matter."
Do you see that?
A. I do.
Q. And in the summary of the claimed subject matter, applicants went through and explained the elements of the claim and where those were supported in the specification, correct?
A. Yes.
Q. And if we look -- start with the paragraph at the bottom of page 64, you see it says "Applicants disclose a method for treating a neurological disease with at least one fumaric acid

derivative, including dimethyl fumarate or monomethyl fumarate, as met before in paragraph 9, lines 9 through 11, and paragraph 62 to 63 in the specification."

Do you see that?

A. Yes.

Q. And if we could turn -- I'm sorry for all the flipping, but file history is, unfortunately, cumbersome.

If you turn to pages 14 and 15, JTX 2173, pages 14 and 15, they have the reference paragraphs 9 and 10.

A. I'm there.

Q. And Method 4 -- is the reference Method 4 the method of treating a neurological disease by administering to the subject in either of at least one compound that is partially structurally similar to DMF or MMF.

And that's what the applicant was pointing out to the examiner, correct?

A. Yes.

Q. And then paragraph 10 on JTX 2173, 15, the applicants were pointing out to the examiner that, in some embodiments, the neurological disease is MS or another demyelinating neurological disease, correct?

A. Yes.

Q. And then that paragraph we had looked at on page 64 also referenced Method 4 in paragraph 62, which is JTX 2173, page 24.

A. Yes.
Q. And this is another disclosure regarding Method 4 wherein it says "Also provided are methods of treating a neurological disease by administering to the subject in need thereof at least one compound that is at least partially structurally similar to DMF and/or MMF," correct?
A. Yes.
Q. And all these paragraphs are also found in the as-issued '514 patent, correct?
A. Yes.
Q. And then if we can return to amendment, if we go to page -- JTX 2173, page 17.

Excuse me. If we could go there -- something that was not cited there is on this page, paragraph 19.

THE COURT: I'm sorry. Where are you?

MR. FELDSTEIN: I'm sorry, Your Honor.

Exhibit JTX 2173, page 17, paragraph 19.

THE COURT: All right.

BY MR. FELDSTEIN:
Q. I'll let you catch up in the page flipping.

There it says "In some embodiments, Method 4 comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound having Formula I, II, III, IV, e.g., a fumaric acid derivative (e.g., DMF or MMF)," correct?

A. Yes.
Q. And that's also found in the as-issued patent, correct?
A. Yes.
Q. Now, if you can turn back to the preliminary amendment and the remarks on page JTX 2173, 65. It's page 7 of the document itself. And the paragraph that begins "Additionally."

And now applicants are pointing out that "Additionally, applicants disclose that DMF and/or MMF are effective in treating MS." For example, DMF and MMF are listed as specific examples of neuroprotective compounds, and then it cites to paragraph 63.

Do you see that?
A. Yes.
Q. And if we turn to that paragraph, which is on JTX 2173, page 24.

And paragraph 63 teaches that "In some embodiments of Method 4, a method of treating a mammal who has or is at risk for neurological diseases is provided. The method comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound which has Formula I, II, III, IV, e.g., a fumaric acid derivative (e.g., DMF or MMF)," correct?
A. Yes.
Q. And so applications are pointing out to the examiner that they disclose that DMF and/or MMF is listed as a specific

treatment for neuroprotect -- as a -- let me start again.

Applicants are pointing out that DMF and MMF are listed as specific examples of neuroprotective compounds, correct?

A. Yes.

Q. And that's in fact what paragraph 63 provides, correct?

A. It does. Well, it describes at least one neuroprotective compound which has -- and it lists the four formulas and examples, fumaric acid derivative, e.g., DMF or MMF.

Q. And paragraph 63 from the original specification is also found in the issued patent, correct?

A. Yes.

Q. And then if we return to JTX 2173, page 65, below the quote that reads "As such, DMF and MMF are specifically named in the application's compounds effective in treating neurological diseases such as MS. Furthermore, the dosages disclosed in paragraph 116 of the application refer to the specific compound DMF and MMF."

Do you see that?

A. I see it.

Q. And if we could turn to JTX 2173, page 40 to 41, where they have paragraph 116. And here, in fact, the application is pointing to DMF and MMF as, again, specific compounds for the treatment of neurological diseases, correct?

A. I'm sorry. What's on the screen, is that what you're referring to?

Q. Yes.
A. So this paragraph is referring to DMF and MMF, "an effective amount can range." In this paragraph, it doesn't discuss anything relative to neurologic conditions.
Q. Okay. It's indicating, however, that the dosages -- the dosages in this paragraph are specific to DMF and/or MMF, correct?
A. So for the first part, "For DMF or MMF, an effective amount can range," and then it lists one, two -- three ranges. So, yes, it lists three ranges of effective doses of DMF or MMF.
Q. Right. It's indicating that DMF -- there are effective doses of DMF or MMF -- correct? -- is what the patent is teaching here, paragraph 116?
A. It is teaching that there is an effective range.
Q. And this paragraph 116 is also found in the issued patent, correct?
A. Yes.
Q. Okay. If we turn back to the preliminary amendment, JTX 2173, page 65, and applicants disclosed -- we'll look at the paragraph, applicants reported to the examiner that they also disclosed that "orally administering 480 milligrams of DMF and/or MMF is effective in treating MS," and they cite to that same paragraph 116, correct?
A. I see that, yes.

Q. And if we go back to the paragraph 116, which is on page 40 to 41, the 480-milligram dose.

Page 40 to 41. Maybe not. Yeah. All the way down at the bottom. Thank you.

The 480 that's being referred to is the 480, three lines up from the bottom, as part of the range of about 480 to about 720 milligrams per day, correct?

A. That's the paragraph it's referring to, yes.

Q. Right. And so the examiner was aware that applicants were relying on the 480 milligram per day as part of this range of 720 as support for the method of treatment of multiple sclerosis with a 480-milligram-per-day effective dose, correct?

A. I'm sorry. Could you repeat the first part of that question?

Q. The examiner was aware that applicants were relying on the disclosure of 480 milligrams within this range as support for the claim to a method of treating multiple sclerosis with a therapeutically effective amount of DMF, that amount being 480 milligrams, correct?

A. I guess the only caution -- they're absolutely aware that it's being listed. I don't know what they relied on specifically. And so they indicate that the applicants also disclose in the list of all the other disclosures. So they're absolutely aware that it's being disclosed for sure.

Q. Applicants are reporting to the examiner, here is our

support for the 480 milligrams in the claim, correct?
A. Yes.
Q. Okay. And the 480 milligrams is part of the narrowest range that's disclosed in this specification for an effective dose of DMF or MMF, correct?
A. So it's -- in this paragraph, when it was giving examples of effective doses, that was the narrowest range. It's not the narrowest range in the specification.
Q. It's the narrowest range of what's indicated to be an effective dose of DMF or MMF to be administered to a subject orally, correct?
A. I'm not sure that's correct.
Q. Okay. Do you want to point me to a narrower recitation of where the patent refers to an effective -- the narrower range for an effective dose of DMF or MMF to be administered to a subject orally?
A. Well, first, I'm not sure where the introduction of this being specifically orally comes from. I don't see the word "orally" or the abbreviations PO, by mouth, at any point. So that's one issue.

But just in terms of ranges, in Column 18, the narrowest range -- and I'd have to work on the math. When you get down to -- let's see. There's one range that's 1 microgram per kg up to 1 milligram per kg, so that's a range of about 60 milligrams. So that's a narrower range than 480 to 720. So

I'm not sure I'd call this the narrowest range that's described.

Q. Okay. Let's look, however, Dr. Greenberg, at what we have on the screen from paragraph 116 in JTX 2173, page 40, 41.

Do you see the sentence four lines down from the top that says "For example"?

A. "For example," yes.

Q. And it says "For example, an effective dose of DMF or" -- correcting the typo -- "MMF to be administered to a subject orally," do you see where it does teach orally, in fact?

A. Yes, you're correct. Excuse me.

Q. And so for an oral dose of -- for an effective oral dose of DMF or MMF, the narrowest range in the specification is 480 to 720 milligrams, correct?

A. So yes, in this paragraph, it's the -- and I apologize for misspeaking earlier.

I guess what I'm saying is the prior ranges, I don't read it as assuming those aren't oral, that this was the only oral dose.

Q. Now I'd like to go back to -- look to the patent itself, JTX 2000. And if you look at Column 1, lines 1 to 20. And I believe you agreed on your direct testimony that the patent does specifically say that "provided are certain compounds for treating neurological diseases, including demyelinating neurological disorders, such as, e.g., multiple sclerosis,"

correct?
A. Yes.
Q. In fact, multiple sclerosis is the first specifically identified neurological condition in the patent, correct?
A. It's the first one identified in this column. In the abstract, I'd have to look back if there are specifically others. This is the first.
Q. Okay. And then the next paragraph, you also referred to in your direct testimony, it starts again and describes more information about multiple sclerosis, correct?
A. Yes.
Q. And what it's describing in the second sentence is characteristics, the disease characterized by. It's describing characteristics of multiple sclerosis, correct?
A. Yes.
Q. And those characteristics are inflammation in parts of the CNS leading to the loss of the myelin sheathing around neuronal axons, demyelination, loss of axons, and the eventual death of neurons, oligodendrocytes, and glial cells, correct?
A. Correct.
Q. And you agree with -- those are characteristics of multiple sclerosis, correct?
A. Yes.
Q. And if we turn to Column 5 in the patent, line 52 to 59, something I think you did not address either in your report or

on your direct testimony, but at 52 to 59, Column 5, there's a paragraph that begins "The terms 'therapeutically effective dose' and 'therapeutically effective amount.'"

Do you see that?

A. I do.

Q. And you do not address this in either your reports in this case or in your direct testimony this morning, correct?

A. I know for sure this morning we didn't call out this specific paragraph. I'd have to look back at my report in detail to know if we did or didn't.

Q. Fair enough.

So I'll begin reading again. "The terms 'therapeutically effective dose' and 'therapeutically effective amount' refer to the amount of a compound which results in at least one of prevention or delay of onset or amelioration of symptoms of a neurological disorder in a subject or an attainment of a desired biological outcome such as reduced neurodegeneration (e.g., demyelination, axonal loss, and neuronal death.)"

And those again are the characteristics of multiple sclerosis that the patent defined and that you agreed with, correct?

A. Yes. The only difference between this sentence and the prior one shown is the prior shown talked about "and eventual neuronal death" after the processes of demyelination and axonal loss.

Q. And we had gone through the preliminary amendment in some detail. And I apologize for that.

But after the applicants amended their claims to include the current Claim 15, for example, and pointed out where they believed a claim was supported in the specification in some detail, you're aware that the examiner never rejected the claims for lack of written description support, correct?

A. So while the examiner didn't reject it, I'm not aware that the examiner ever specifically stated that the specifications had written descriptions, but I know that the patent obviously went through the examiner.

Q. And it went through without any rejection by the examiner questioning the written description support after applicants laid out where the support came from, correct?

A. My understanding -- and I'd have to go through it to find the details -- is that, after that back-and-forth, the patent went through but without a distinct obvious negation of written description but, on the other side, a specific endorsement of that written description existed.

Q. Okay. And you had gone in your direct testimony on Tuesday, some of your expertise. I take it you don't profess to have any expertise in interpreting written description superior to a patented examiner.

Is that fair to say?

A. I approach written description from a person skilled in

the arts, not from the approach of a patent examiner.

Q. But to stay in the patent and turn to the examples, you discussed the examples in some detail. And I'd like to turn to Example 3, which is -- it begins in column -- the very bottom of Column 20, line 60, and then it continues through line 15 of Column 22.

You had indicated that this EAE model is a live mouse model, correct?

A. Correct.

Q. And in this live mouse model -- and by "model" it means disease model? It's a real, living mouse?

A. It's a real, living mouse, yes.

Q. And in this mouse model, what was done was DMF and MMF were administered to separate mice, correct?

A. Correct.

Q. And the range -- the low end of what DMF was added was 5 milligrams per kilogram body weight DMF twice a day, and that's Column 21, line 7 or so?

A. Yes.

Q. And then the high amount of DMF was 15 milligrams per kilogram body weight DMF, correct?

A. Yes.

Q. And those were administered in BID dosing, twice a day, correct?

A. Yes.

Q. And the range -- very simple math, the range from 5 to 15 is a factor of three, correct?
A. Yes.
Q. And across this factor of three, what Example 3 shows is that there was NRF2 activation at both the low-dose range and the high-dose range, correct?
A. Yes.
Q. And so, at the very least, this Example 3 indicates that the range for activating NRF2 in the mouse model is not a narrow range; it's at least a threefold range of dosing. Correct?
A. Not completely.

I guess the one issue that we're leaving off is that the Figure 3 is a qualitative figure, not a quantitative figure. So I think a skilled artisan, when reading this, would be able to say yes/no, there appears to be some activation or not.

And relative to a threefold change in the dosing, a skilled artisan would look at this and say, within those ranges, we get yes activation but can't quantify a response.

Q. So that's fine. So binary activation, yes/no across at least a threefold range of doses administered BID, is disclosed in Example 3?
A. Specifically, just activation of the NRF2 pathway, of what they're staining for in Figure 3, yes.
Q. Okay. And we had talked about earlier the 720-milligram

dose that was known to be effective for treating multiple sclerosis in humans, correct?

A. Yes.

Q. And the difference between 720 and 480 milligrams is much less than a factor of three, correct?

A. It is less than a factor of three.

Q. You also spoke about the declaration of Dr. Dawson. Do you recall?

A. Yes.

Q. And if we could go back -- and I apologize that we are going back to the big book, but it's Exhibit 2173. And I think that you had looked at page 237. I think you had looked at paragraph 16 on page 237.

A. I can see it on the screen, yes.

Q. This is what you'd referred to in your direct testimony, correct?

A. Yes.

Q. And this is -- if you can flip to the next page, this is the last substantive paragraph, paragraph 16, in the entire Dawson declaration, correct?

A. Yes.

Q. And I actually -- I hadn't expected you to rely on paragraph 16 because I think that, in your reports, you had relied on paragraph 14. And if we can look at that, if you don't mind. It's one page earlier, page 236. And it refers to

the positive and clinically meaningful results in paragraph 14.

Do you see that?

A. Yes.

Q. And I think you were referring in your testimony, maybe in the context of paragraph 16, to the -- Dr. Dawson's testimony that the positive and clinically meaningful results obtained with 480-milligrams-per-day dose of DMF were unexpected, correct?

A. Yes.

Q. And this is again still -- you looked at the very last paragraph. Paragraph 14 is still part of the summary of the 19-page document, correct?

A. Yes.

Q. And the rest of it, the earlier pages, give context for what Dr. Dawson means by positive and clinically meaningful results, don't they?

A. That's my understanding.

Q. So if we can go earlier in Dr. Dawson's declaration to page 2173, page 227, paragraph 12.

A. I'm sorry. Could you repeat the exhibit numbers. I don't have it in front of me.

Q. It's all 2173 right now, which is the file history, and we're going to go to page 227, please.

A. Thank you.

Q. Are you with me?

A. Thank you.
Q. And we're in paragraph 12. And paragraph 12 is where Dr. Dawson is starting to refer to what -- the positive and clinically meaningful results that she then references in the summary, correct?
A. Yes.
Q. And these are the positive and clinically meaningful results from Biogen's Phase 3 studies of 480, 720 milligrams of DMF to treat MS, correct?
A. Yes.
Q. And what Dr. Dawson says is -- in paragraph 12, "As shown below, the results at two years of the Phase 3 clinical trial demonstrated that both the 480-milligrams-per-day dose and the 720-milligram-per-day dose regimens versus placebo met all primary and secondary end points with a high level of statistical significance and that both doses demonstrate efficacy in the defined trial."
Correct?
A. That's what it says, yes.
Q. And so that is part of what Dr. Dawson is referring to as the unexpected -- unexpected positive and clinically meaningful results, correct?
A. Yes.
Q. Okay. And then if we look on the next page, page 228, she starts to enumerate what all the specific data are, correct?

A. Yes.
Q. And in paragraph A on page 228, she reports that "Compared to placebo, patients administered 480 milligrams per day or 720 milligrams per day exhibited a 90 percent or a 73 percent respectively decrease in the number of new Gd lesions for two years, as shown in Figure 4 below."
Right?
A. Yes.
Q. And these are again the positive and clinically meaningful results that were unexpected, correct?
A. Yes.
Q. And what she shows here in Figure 4 is a 90 percent decrease in the mean number of Gd lesions in the Phase 3 trial for 480 milligrams, correct?
A. Yes.
Q. And if we move forward, there are still more explanation and context for what positive and clinically meaningful results were unexpected from Dr. Dawson, correct?
A. Yes.
Q. And we can turn to page 229, paragraph B. And in page 229, paragraph B, Dr. Dawson reports the data that "patients administered 480 milligram per day (240 milligram BID) DMF or 720 milligrams per day (240 TID) DMF, also exhibited a decrease in Gd lesion volume as shown in Figure 5 below," correct?

A. Yes.
Q. And then Figure 5 shows the middle bar in each set. The one-year set on the left and the two-year set on the right shows a decrease in Gd lesion volume for the 480-milligram-per-day dose relative to placebo, correct?
A. Correct.
Q. And these are again part of the positive and clinically meaningful results that Dr. Dawson found unexpected, correct?
A. I assume so.
Q. And there are still more context and specific positive and clinically meaningful results reported by Dr. Dawson before she gets to her summary, correct?
A. There are more results reported, yes.
Q. So if we can go to page 230, paragraph C. And in paragraph C on page 230, Dr. Dawson reported that "patients administered 480-milligrams-per-day DMF or 720-milligrams-per-day DMF exhibited an 85 percent or 74 percent, respectively, decrease in mean number of new and enlarging T2 hypointense [sic] lesions developed over two years, as shown in Figure 6 below," correct?
A. Correct.
Q. So, again, that's shown in the middle column in Figure 5. This is another example, another specific example, of what positive and clinically meaningful results Dr. Dawson found unexpected, correct?

A. These are positive results that she found meaningful, yes.
Q. Right. And it's the positive and clinically meaningful results that she reports in this summary are what she found unexpected, correct?
A. So I will just note that all the data we're talking about thus far is MRI data, which is a surrogate measure we use. I can't parse out if Dr. Dawson is relying on this for the term "clinical" or if she's specifically referring to things such as the annualized relapse rate or something else.

So I don't want to read into which part she's referring to, but it is encompassed in the report that precedes the conclusion she makes, the summary that she makes.
Q. Okay. And so we won't go through every one, but we'll just flip through, if you don't mind, part -- and on page 231, paragraph D, another part of the unexpected results that Dr. Dawson is referring to is the effect of 480 milligrams on T2 lesion volume, correct?
A. Correct.
Q. And then if we turn to page 232, another clinical trial result that Dr. Dawson reports and relies on is T1 hypointense lesions, correct?
A. Yes.
Q. And then if we turn to page 233, another clinical trial result that Dr. Dawson relies on for her conclusion is the effect of 480 milligrams on T1 hypointense lesion volume,

correct?
A. Yes.
Q. And then if we turn to page 235, and perhaps to your point, Dr. Dawson also includes, as the positive and clinically meaningful results in paragraph H, that "480 milligrams and 720 milligrams of DMF reduced the risk of relapse at two years by 49 percent and 50 percent, respectively, compared to placebo," correct?
A. Yes.
Q. And so these are, again, part of the results that Dr. Dawson is relying on as unexpected positive and clinically meaningful results?
A. Yes.
Q. And I think, lastly, I'd like to know, on this same page, paragraph I, it says "Another unexpected positive and clinically meaningful result that Dr. Dawson relied on is that patients administered 480-milligrams-per-day DMF and 720-milligrams-per-day DMF exhibited a statistically significant decrease in the progression of confirmed disability at 12 weeks as compared with patients administered placebo, as shown in Figure 11 below," correct?
A. Correct.
Q. And that, in fact, Figure 11 below, in fact, shows that 480 milligrams reduced the progression of disability relative to placebo, correct?

A. Correct.
Q. I think you can put aside Exhibit 2173 for now, Doctor.
I'd like to turn in the other volume we gave you, Doctor, to PTX 188.
PTX 188 is a patent application where you're a named inventor, correct?
A. Yes.
Q. If you could turn to the claims which are on page 26 of PTX 188.
A. Yes.
Q. And you're claiming -- and I may skip parts of it that are complicated to read; but, basically, you're claiming a method of treating an antibody-mediated autoimmune disease, correct?
A. Yes.
Q. And the first step is determining a nucleotide sequence, correct?
A. Yes.
Q. And the second step involves identifying one or more nucleotide sequences, correct?
A. Yes, sir.
Q. And then the next step involves synthesizing one or more oligonucleotides, correct?
A. Yes.
Q. And the final step is administering the one or more oligonucleotides, correct?

A. Yes.
Q. And so your claims cover, as drafted here, any antibody-mediated immune disease, correct?
A. I'm sorry. Can you repeat that?
Q. Your claims are not limited to any specific antibody-mediated immune disease -- autoimmune disease, correct?
A. In this claim, it just says "A method for treating an antibody-mediated autoimmune disease."
Q. All right. They're not limited to any specific autoimmune disease, correct?

MS. BLOODWORTH: Objection, Your Honor. Relevance. I'm not sure why we're going into his patent application.

THE COURT: I was wondering the same thing.

MR. FELDSTEIN: Your Honor, I think we can show some inconsistency between Dr. Greenberg's testimony of all the things he would be looking for in the '514 patent compared to what he discloses.

He discloses no examples of any of the things that he's claiming, no examples of determining a nucleotide sequence.

THE COURT: This is a patent that has been issued or --

MR. FELDSTEIN: It's been applied for, Your Honor.

THE COURT: It's been applied. So it's pending.

MR. FELDSTEIN: Sure. But it's still his opinion on -- I think it relates, Your Honor, to his opinion on what one needs to teach.

THE COURT: Does this have anything to do with MS or DMF?

MR. FELDSTEIN: It does have to do with MS, Your Honor.

THE COURT: Where?

MR. FELDSTEIN: If we go to -- we've asked the witness. I think the witness will agree that it is --

THE COURT: I think that this is the first time I've seen this, but under "detailed description of the invention," I see MS.

MR. FELDSTEIN: Yeah. And if we look at Claim 38, which is on page 30.

THE COURT: I don't need to know a lot about this. If you'd like to --

MR. FELDSTEIN: It's very short, Your Honor. Thank you.

BY MR. FELDSTEIN:

Q. So you're claiming -- you've reported and your claim covers a method of treating an antibody-mediated immune disease that includes multiple sclerosis, correct?

A. Yes.

Q. You don't report any example of determining a nucleotide

sequence to the setting, correct?

A. So, as I came here today to be a skilled artisan to talk about the '514 patent, I have to be honest, I haven't reviewed the skilled art or this patent which was filed as of, I believe, 2017 or earlier.

And so I'm not sure I'm prepared to go through written description here relative to this patent where I'm the inventor, which is a little different than looking through it through the lens of somebody who's not the inventor and just a skilled artisan. So I'm not sure I'm prepared to answer that question.

If you want me to take time and read through and really understand the depths of your questions, I can work through this, but I didn't come here prepared to talk about my patent.

Q. Let me ask you -- this may be an easier question for you to answer.

But, first, this patent came up at your deposition in this case, correct?

A. This came up with the question of am I trying to compete with Biogen and am I biased because I have a company that has a patent that may work in multiple sclerosis.

And in the deposition I answered that our early-stage company, which has nothing in trials which is unfunded and, hopefully, we'll get there, is not a competitor in any way, shape, or form, and this patent has nothing to do with small

molecules, DMF, the NRF2 pathway, or anything specific to Tecfidera in any way, shape, or form.

And we ended that conversation after feeling as though there wasn't a bias based on my interest in the company.

Q. So the short answer is, yes, it came up at your deposition, this patent, PTX 188, correct?

A. In the context of potential bias.

Q. So yes?

A. So, yes, in the context of potential bias.

Q. And can you agree with me, Dr. Greenberg, that within PTX 188, you don't have even one specific example of an oligonucleotide that could be used in the method that you're describing?

A. To my recollection. And, again, having not prepared to discuss this, I don't recall the specific example of an oligonucleotide.

Q. Do you recall that there are no working examples of the method, correct?

A. Again, I'd have to review it to answer in any degree of confidence that I'm giving you accurate answers.

Q. And do you recall that there are no prophetic examples of clinical trials in here?

A. Again, I'm not in a position to answer specifics unless I have the time to review things and go through it and understand it.

MR. FELDSTEIN: Okay. We move to admit PTX 188.

And that's all we have for you, Dr. Greenberg. Thank you.

THE COURT: Just a minute.

Is there any objection to the admission of 188?

MS. BLOODWORTH: No, Your Honor.

THE COURT: All right. The Court admits PTX 188 but with some caution. I'm going to always look at this as impeachment, not as substantive evidence in this case. It has absolutely nothing to do with this patent. And, as I understand it, you're seeking to undermine or to impeach his testimony on the basis that not even he did everything that he could -- that he thinks that Biogen should have done and for which he criticized.

MR. FELDSTEIN: That's right, Your Honor.

THE COURT: Why is that coming in?

MR. FELDSTEIN: Just because the witness couldn't recall answers to certain questions, we want to have the record document --

THE COURT: That doesn't give you a basis for substantive evidence. I'm letting it in because there's no objection, but I'm letting it in solely because it was impeachment and you want it in, but I'm not going to look at it as substantive evidence. And that's on the record.

MR. FELDSTEIN: Understood, Your Honor. Thank you.

THE COURT: I don't want this record cluttered up with impeachment. This is what I've been saying from the get-go. So you moved it in on him. But to me it's classical impeachment. I would never keep you from asking him these questions, and I don't know why Mylan isn't objecting.

MS. BLOODWORTH: I object now, Your Honor.

THE COURT: No, it's a little late.

I just want to note for the record that there used to be a federal judge in the Eastern District of Virginia named "Roarin' Oren" Lewis, and not anybody that I ever knew in my time, but I heard a lot about him. And when he didn't think something was going right, there being no video or cameras or anything, he would start moving one side or the other, "Where's the objection?"

I haven't done that, but I'm just being very candid. I'm only going to look at it in terms of weight for impeachment.

MR. FELDSTEIN: That's all we need it for, Your Honor. Thank you.

THE COURT: You're welcome.

Any redirect?

MS. BLOODWORTH: Very brief, Your Honor.

THE COURT: Good. After that we'll take our morning recess.

By the way, Roarin' was not his first name. That was

his nickname.

REDIRECT EXAMINATION

BY MS. BLOODWORTH:

Q. Hi, Dr. Greenberg. You were asked on your cross-examination a series of questions about Example 3 and whether that shows that the NRF2 pathway was activated in the EAE mice, if you recall that, over a threefold range?

A. Yes.

Q. Okay. And you said it was?

A. Yes.

Q. Okay. But does Example 3 show that MS is treated in EAE mice over that threefold range?

A. No. So what is laid in the specification -- in order to show treatment in EAE, one would look for a clinical or histopathological result showing protection of myelin or axons.

As a very basic level, EAE, to judge a clinically effective amount, you have to show that the mouse does better on your compound versus a control, whether their paralysis goes away or is prevented.

And none of that is embodied in Example 3. It reads purely as a way to screen for NRF2 activation, but that is a far cry from a therapeutically effective amount for a mouse with EAE.

Q. And I think you were also asked a series of questions about paragraph 116 in the file history, which is page 40 of

Exhibit 2173.

A. Yes.

Q. And I think you were asked a series of questions about whether or not paragraph 116 in the application and its corresponding paragraph in the patent discloses an effective range.

A. Yes.

Q. And I think your answer was that it does. And that's because the paragraph uses the word "effective amount," correct?

A. Yes.

Q. Do you think that this paragraph discloses an effective range of a 1-milligram-per-kilogram dose of DMF?

A. No.

Q. Therapeutically effective range?

A. No. It states an effective amount. It doesn't discuss that range.

Q. Is there anything in paragraph 116 that discloses a therapeutically effective amount for treating MS?

A. No.

Q. And you were asked a series of questions about Dr. Dawson's declaration.

Do you recall?

A. Yes.

Q. And your understanding is that Dr. Dawson submitted her

declaration after receiving the defined clinical Phase 3 trial results in 2011, correct?

A. Yes.

Q. And Dr. Dawson opined that, as of 2011, a skilled artisan found that a 480-milligram worked was unexpected.

Is that your understanding?

A. Yes.

Q. You also reviewed in this case the expert reports of doctors Wynn and Duddy, correct?

A. Yes.

THE COURT: How far beyond the direct --

MS. BLOODWORTH: I'm sorry, Your Honor.

BY MS. BLOODWORTH:

Q. I just want to say and so Dr. Dawson's declaration, as well as the others, is what you were relying upon for your understanding that -- your arguments in the alternative to those statements that it was unexpected?

A. Yes. Dr. Dawson clearly states that a skilled artisan would not expect 480 milligrams to work.

THE COURT: That was a lovely cross-examination on your redirect.

MS. BLOODWORTH: I'm sorry, Your Honor.

THE COURT: I should say leading. Okay. Thank you.

MS. BLOODWORTH: I was trying to go quickly.

THE COURT: Anything further?

MR. FELDSTEIN: No, Your Honor. Thank you.

THE COURT: Thank you. All right. Thank you, Dr. Greenberg. You may step down. I believe you're excused as a witness, at least by me.

THE WITNESS: Thank you, Your Honor.

THE COURT: The Court will stand in recess for -- is 15 working for everybody? Take 15 minutes. We'll resume at 11:00. Thank you.

(Recess taken, 10:45 to 11:00.)

THE COURT: Any more witnesses for Mylan in its case in chief?

MR. ANSTAETT: Your Honor, the only witnesses will be presented via deposition, Dr. Dawson, Dr. O'Neill.

THE COURT: At this time you may call your next witness.

MR. BROWNING: Yes, Your Honor. That's us. Paul Browning, counsel for Biogen. We're going to call the next witness.

THE COURT: So Mylan is adopting some of this testimony in its case in chief, but Biogen is putting a witness on?

MR. ANSTAETT: No, Your Honor. Just because we know Dr. Wynn wants to get up and get down --

THE COURT: So Dr. Wynn at this time?

MR. ANSTAETT: -- we're happy to have them --

MR. BROWNING: Yes, Your Honor.

THE COURT: Dr. Wynn, would you please approach the clerk, who will administer the oath to you before you take the witness stand, sir.

THE CLERK: The witness is Dr. Daniel Wynn, W-Y-N-N.

THE COURT: Dr. Wynn, good morning. Welcome to our wintery weather here in West Virginia.

THE WITNESS: Thank you.

THE COURT: You my proceed.

MR. BROWNING: May I approach with binders?

THE COURT: You may.

DANIEL WYNN, **PLAINTIFFS' WITNESS, SWORN**

DIRECT EXAMINATION

BY MR. BROWNING:

Q. Good morning, Dr. Wynn.

A. Good morning.

Q. Could you please state your name and address for the record.

A. Daniel Wynn, MD. My office address is 1535 Lake Cook Road in Northbrook, Illinois.

THE COURT: I take away my apologies for the weather. Your weather has to be this bad or worse, right?

THE WITNESS: Yes, Your Honor.

THE COURT: At least right now. Okay. Thank you.

BY MR. BROWNING:

Q. And referring to the first demonstrative, Doctor, we'll have to make an amendment to the first demonstrative because there was no testimony on the issue of enablement, correct?

A. Correct.

Q. So leaving aside the second bullet point, could you inform the Court as to what issues you're here to address today.

A. Yes. I've been asked to speak to whether or not the '514 patent specification provides written description support for the claims.

Q. Thank you, Doctor. And I'd like to ask you first some questions about your background.

And can you please tell us who is your current employer.

A. Consultants in Neurology, by Chicago.

Q. What is Consultants in Neurology?

A. Consultants in Neurology is a large, single-specialty neurology practice.

Q. And what is your job title with Consultants in Neurology?

A. Partner and the director of the multiple sclerosis center, member of -- a comprehensive care center for the National Multiple Sclerosis Society, and a member of the Consortium of Multiple Sclerosis Centers.

Q. And can you explain for us your duties and responsibilities in that position.

A. Yes. My responsibilities, I see patients Monday through

Saturday; supervise our research staff as the director of the center for clinical research, the physicians, nurses, other allied health professionals; teach medical students; and the like.

Q. Okay. And at which school do you teach medical students?

A. I teach both students and trainees at the Chicago Medical School as well as at Midwestern University, the Chicago College for Osteopathic Medicine.

Q. How long have you been employed by Consultants in Neurology?

A. I've practiced at Consultants in Neurology for approximately 32 years.

Q. If we could go to your binder of exhibits and go to the first exhibit, which is PTX 643. Could you identify that for us?

A. Yes. This exhibit is my curriculum vitae.

Q. Does this accurately describe your education, work experience, and scientific work and accomplishment?

A. It does at the time it was presented. There are some additional publications and presentations since this was made, but the new things do not specifically represent or refer to the patented claims.

Q. Okay. And I'd like to ask you about some of those details.

And, for the record, we are we displaying PDX 3-3, a

demonstrative.

Do you have a medical degree, Doctor?

A. Yes. I have a medical doctor from the Chicago Medical School.

Q. Did you receive additional medical training after medical school?

A. Yes, I did. I went on to Rochester, Minnesota, colder than even here or Chicago, where I did fellowships in internal medicine and neurology. I did subsequent fellowship-level work in neurophysiology, epilepsy, neuromuscular disease, as well as a fellowship in sleep disorders medicine.

Q. Doctor, are you board-certified in any area of medicine?

A. I am. I am board-certified by the American Board of Psychiatry and Neurology in neurology.

I am board-certified by the American Board of Psychiatry and Neurology, and special competence in clinical nerve physiology.

I'm board-certified and a fellow in sleep medicine by the American Board of Sleep Disorders Medicine.

I'm board-certified and a fellow in clinical nerve physiology by the American Board of Neuromuscular and Electrodiagnostic Medicine.

Q. In your medical practice, do you treat patients with multiple sclerosis?

A. Yes. That's my full-time job.

Q. And how many patients, approximately, do you treat each year?
A. Each year I see approximately 1500 individuals living with multiple sclerosis.
Q. And do you have any experience in assisting with clinical trials of drugs for the treatment of multiple sclerosis?
A. I do. I've been investigator -- primarily principal investigator in over 200 clinical trials in neurology, over 85 in multiple sclerosis.
Q. And have you authored any scholarly articles relating to your work on multiple sclerosis?
A. I have. I've published over 135 peer-reviewed manuscripts, book chapters, and abstracts relating to neurology, predominantly regarding multiple sclerosis.
Q. And, for the record, we're displaying some of these details on PDX 3-4.

Do you work with any advocacy associations for patients suffering from multiple sclerosis?
A. I do. I'm proud that I've been active volunteer for the National Multiple Sclerosis Society, the primary advocacy society nationally for individuals with multiple sclerosis, the largest provider of funding for multiple sclerosis research outside the government; as well as the MS Association of America and the Multiple Sclerosis Foundation.
Q. Do you do any work for the State of Illinois?

A. I do. I've served through the secretary of state on the Illinois Medical Advisory Board for over ten years, and previously I've also been on formulary committees for the State of Illinois.

Q. For the record we're going forward to PDX 3-5.

Have you received any awards or distinctions in connection with your medical work?

A. I have. As regards to my work with the National Multiple Sclerosis Society, I was honored years ago as the volunteer of the year in the greater Illinois chapter for community service. I was given the valedictorian award through Deloitte & Touche for the Multiple Sclerosis Society for, again, advocacy work and fund-raising for multiple sclerosis research and assisting individuals living with this disease.

I was awarded the Melvin Leichtling Annual Research Award for immunology/oncology that I performed.

Q. Have you worked as a medical director for any professional sports teams?

A. Yes. For over a dozen years I was the medical director for one of the professional hockey teams in Chicago, the Chicago Wolves.

Q. Have you previously testified as an expert witness at trial?

A. I have.

Q. And have you testified for brand or generic companies?

A. Both companies.
Q. Okay. And did you recently testify in the district of -- U.S. District Court in Delaware?
A. I have.
Q. Okay. And were you previously qualified as an expert in neurology and the treatment of multiple sclerosis?
A. Yes.
MR. BROWNING: And at this point, Your Honor, we offer Dr. Wynn as an expert in the field of neurology and in particular the treatment of multiple sclerosis.
THE COURT: Is there any objection?
MR. ANSTAETT: No objection, Your Honor.
THE COURT: The Court will accept Dr. Wynn as an expert in the area of neurology and the treatment of multiple sclerosis and allow him to opine in those areas, but I seriously question his judgment with regard to professional hockey teams. We happen to be big Penguin fans down here. And you already knew that.
You may proceed.
MR. BROWNING: I'm not going to comment on my hockey allegiances. Thank you, Your Honor.
BY MR. BROWNING:
Q. Let's please turn, Doctor, in your binder to the next exhibit, JTX 2000, the '514 patent.
And do you recognize this document, Doctor?

A. I do recognize this document.
Q. Did you review this patent in forming your opinions in this case?
A. Yes, I did.
Q. Okay. And in reviewing the patent, did you form an opinion as to who is a person of ordinary skill in the art to which the patent is directed?
A. I did.
Q. We have -- for the record, we are displaying PDX 3-6.

Can you explain to us the opinion of a person of ordinary skill in the art that you applied in your analysis in this case?
A. Yes. I consider person of ordinary skill in the art in 2007 would have at least a medical degree with at least three years of training in neurology and at least three years of clinical experience in treating multiple sclerosis.
Q. Thank you, Doctor.

Let's go to the claims of the '514 patent. If we could display on the screen Claim 1.

And, Doctor, while we're putting that up, do you have an understanding of the invention disclosed and claimed in the '514 patent?
A. I do.
Q. And in reference to Claim 1, can you generally explain the elements of the claimed invention, as you understand it?

A. Yes. As I understand it, there are three principal claims: One, treating a subject in need of treatment for multiple sclerosis, so treating multiple sclerosis; two, with the use of dimethyl fumarate, DMF and/or MMF, monomethyl fumarate, at a dose of 480 milligrams given daily.

Q. Thank you, Doctor. Let's go to the next demonstrative.

And are we displaying here representative Claim 15? Does this identify the three elements of claimed invention that you just testified to?

A. Yes, it does.

Q. Okay. And does this slide, for the record, PDX 3-7, does this also identify the asserted claims in this case?

A. It does.

Q. For the record, those are?

A. The asserted claims are Claims 1 through 4, 6, 8 through 13, and 15 and 16.

Q. Let's go to the next demonstrative. For the record, it's PDX 3-8.

What are you showing on this demonstrative, Doctor?

A. In Claim 1 is an independent claim regarding, again, the treatment of multiple sclerosis by orally administering a pharmaceutical composition consisting, essentially, of a therapeutically effective amount of dimethyl fumarate, monomethyl fumarate, or a combination, with one or more pharmaceutically acceptable excipients at a dose of

480 milligrams per day.

Dependent Claim 2 was a method of Claim 1 where the dose form is a tablet, a suspension, or capsule.

Claim 3, separate administrations of two, three, four, or six equal doses.

Claim 4, a method of Claim 3 with separate administrations of two equal dosages.

Claim 6, dimethyl fumarate or one or more pharmaceutically acceptable excipients.

Claim 8, again, the method of Claim 1 where the drug is administered to the subject for at least 12 weeks.

Claim 9, a method of Claim 6 where the drug is administered in two separate equal dosages.

And Claim 10, a method of Claim 9 administered to the subject for at least 12 weeks.

Q. And let's go forward for the record to PDX 3-9. And can you explain that additional elements of the independent and dependent claims shown on the slide.

A. Yes. So independent Claim 11, again, treating multiple sclerosis by orally administering about 480 milligrams per day of dimethyl fumarate, monomethyl fumarate, or a combination thereof.

Claim 12 and 13, dependent claims.

Claim 12, dependent upon Claim 11 with a dose of 480 milligrams of dimethyl fumarate.

Claim 13, separate administrations of two equal dosages.

Independent Claim 15, again, treating multiple sclerosis by orally administering to the subject a pharmaceutical composition consisting essentially of a therapeutically effective amount of dimethyl fumarate and one or more pharmaceutically acceptable excipients, again at a dose of 480 milligrams per day.

And dependent Claim 16, by the method of Claim 15, again, two equal dosages.

Q. Thank you, Doctor.

In your opinion, are the asserted claims of the '514 patent embodied by any commercially available products?

A. In my opinion, it is.

Q. What product is that?

A. Tecfidera.

Q. Okay. We're going to discuss in detail your written description opinion in this case, but before we do that I'd like to discuss just a few background topics first.

And we've heard some testimony on this; so I don't want to belabor the point. But can you explain for us again what is multiple sclerosis.

A. Yes. Multiple sclerosis is the most common cause of nontraumatic disability in young individuals, hence the old term the great crippler of young adults.

As has been discussed, there's an autoimmune attack

attacking healthy nerves. So on the demonstrative on the left, there's a normal healthy nerve with a cell body with single branch or axon, we call it, coming off of it, which passes on to a next nerve with the purple, the myelin sheathing, insulating that nerve.

In multiple sclerosis, the myelin sheath is attacked, leading to decreased conduction to the nerve. The myelin not only helps the nerve conduct effectively at a speed of over 50 meters a second -- without myelin, less than a few tenths of a meter a second -- but the myelin also nourishes the nerve and keeps it alive, and loss of myelin leads to death of nerves.

Q. Let's go to the next -- that was, for the record, PDX 3-10 you were referring to. And now we're going to PDX 3-11.

And can you explain to us briefly the type of damage or disability that multiple sclerosis disease can cause.

A. Yes. I sort of think of the brain as our master fuse box. And depending on which nerves are affected, different parts or functions of the body will be affected. If the nerve to the right eye is affected, optic neuritis, one will lose vision in that eye. In the brain stem, vertigo, double vision, imbalance. Spinal cord, trouble using one's hands or trouble walking. Paraplegia, for example, loss of bladder or bowel control, sexual function.

So as many functions as our body can do that are controlled by the brain or spinal cord can be affected by this

terrible disease.

Q. Okay. Thank you, Doctor.

And let's -- one more slide on this topic. How do doctors use -- physicians such as yourself use magnetic resonance imaging methods to track the damage associated with multiple sclerosis?

A. As we discussed in the cartoon, MS is characterized by inflammation in the brain. And we can visualize this in individuals who are alive today by looking at MRI scan. On the image on the left, the large white ball towards the top on the right is the area of active inflammation.

Upon administering of Gd, gadolinium, contrast agent on a T1 sequence, you can see areas of active inflammation in white there. Areas that were affected in the past but are not necessarily active will be seen on T2 sequences. So you do see that big bright spot, as seen in the image on the left, but also other areas of the brain affected as well.

When the areas of inflammation are particularly severe, such as in this case on T1 without contrast, there's what we call a black hole, T1 hypointensity, or up to 40 percent of the matrix of the tissue of the brain in that area is now dead or lost.

So, again, MS is characterized by demyelination, nerve fiber, brain cell loss. And we can see this in individuals living with this disease. And it's a way that neurologists use

to diagnose MS and also to follow the course of the disease and response to treatment.

Q. Put more simply, Doctor, these images show lesions on the brain that are associated with multiple sclerosis?

A. Yes. These are scars. Clearly, one of our goals in treatment is to decrease the number of scars that people get in their brain.

Q. Thank you, Doctor. One more background topic.

You were here this morning to see Dr. Greenberg testify, correct?

A. I was.

Q. And did you hear Dr. Greenberg testify that, as of February 2007, the priority date of the '514 patent, persons of ordinary skill in the art knew that a dosage of 720 milligrams per day of dimethyl fumarate was effective in treating multiple sclerosis?

A. I did hear him say that, and I agree.

Q. Thank you, Doctor.

And let's go -- just go briefly to the next exhibit, which is JTX 2153B.

And do you recognize this document, Doctor?

A. I do recognize it.

Q. Why don't we put the first page on the screen.

Briefly, what is this document, Doctor?

A. This is the first slide in a presentation from Biogen,

O'Neill's presentation, presented by Professor Kappos, of the Phase 2 trial of dimethyl fumarate in the treatment of relapsing multiple sclerosis.

Q. Okay.

A. The Phase 2 study.

Q. Thank you, Doctor.

And if we could jump forward to the Bates page ending at 210. It's about the third or fourth page of the document.

What drug product was being tested in this Phase 2 study?

A. In this study, dimethyl fumarate was being studied in enteric-coated microtablets.

Q. Okay. And is this document what informed one -- in your opinion, one of ordinary skill in the art, in 2007, that a dosage of 720 milligrams of dimethyl fumarate was effective in treating multiple sclerosis?

A. Later in this presentation, there's a slide which shows that, indeed, 720 milligrams was an effective dose.

Q. Okay. And is that -- just for the record, is that going to be shown at least on slide -- Bates page ending in 217?

Yes. We have it on the screen.

Is this the slide you were just referring to, Doctor?

A. Yes.

Q. Okay. Let's now turn in detail to your written description opinion.

So, again, you were here to see Dr. Greenberg testify.

And you heard his opinions concerning the written description requirement, correct?

A. I did.

Q. And did you agree with Dr. Greenberg's testimony that the '514 patent does not describe the claimed invention?

A. I did hear him say that. And, respectfully, I disagree.

Q. And, just briefly, why do you disagree?

A. It is my feeling that the specification of the '514 patent fully describes the claimed elements in the '514 patent.

Q. Thank you, Doctor.

And let's go back to the demonstratives.

And, Doctor, have you assessed whether the '514 patent claims meet the written description standard under the United States patent laws?

A. Yes. My understanding is, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Q. Okay. And let's now dive into the substance.

We previously discussed how, in your opinion, the claimed invention has three elements. Can you remind us of those three elements?

A. Yes. The three elements are treatment of multiple sclerosis; two, with dimethyl fumarate or monomethyl fumarate;

and, three, a dose orally of 480 milligrams per day.

Q. Okay. So let's go back to the '514 patent. Just for the record, it's JTX 2000. And let's talk about the first element, treatment of multiple sclerosis.

And let's go to Column 1, lines 12 through 14, of the '514 patent. And can you explain to us, Doctor, what is being described here?

A. In Column 1 of the '514 patent are several -- the first substantive paragraphs of this patent are describing multiple sclerosis.

Q. And does the patent continue in its discussion of multiple sclerosis at lines 15 through 52 of Column 1?

A. It does.

Beginning on line 15, it simply mentions that multiple sclerosis, as has been discussed, is an autoimmune disease. The activity against tissue in the central nervous system, the brain and spinal cord, where there's, again, inflammation leading to demyelination, loss of axons, and eventual death of nerves, oligodendrocytes, and glial cells, again, the kinds of things that we can infer from looking at the MRI imaging that we looked at a moment ago.

The next substantive paragraph lists the epidemiology of multiple sclerosis. At this time, it was felt that approximately two and a half million people worldwide had the disease, primarily affecting individuals in their youth,

between 20 and 40, the ages where people are having families, becoming married, of course, starting their careers. Hence the old name for MS, "The great crippler of young adults."

Most commonly, the disease presents with a relapsing-remitting course. Over the course of several days, two weeks, a new symptom may appear, weakness, numbness, visual loss, or others. Untreated, this will go on for weeks to months. With treatment, sometimes these symptoms may go away more quickly; but, unfortunately, commonly, not completely.

Q. Thank you, Doctor.

And just to be absolutely clear, if we look at Column 1, lines 15 through 20, does the patent here provide a description of the characteristics of MS?

A. It does.

Specifically, the characteristics are the loss of the myelin sheathing around the nerves, demyelination, loss of axons and eventual death of neurons, oligodendrocytes, and glial cells.

And, again, these lines are repeated many times throughout the patent. And these are the kinds of findings we see in MS that, really, any student in medicine would recognize very quickly are the hallmark findings of this disease.

Q. And to be fair, Doctor, are other diseases mentioned in the '514 patent?

A. Yes, there are.

Q. Does that detract from your opinion that there's an emphasis on multiple sclerosis?
A. Not at all.
Q. And let's go to Column 2, line 60, and extending over to Column 3, line 9.

And can you please explain for us, Doctor, what's being described in this portion of the patent.
A. Yes. The patent describes five methods. They really fall into two buckets.

Methods 1 through 3 are, as have been described, methods of screening for a new compound candidate, methods for evaluating its neuroprotective properties to, for example, prevent the kinds of damage we were talking about earlier. 3, for comparing its equivalence -- an individual compound with another compound.

The second buckets are Methods 4 and 5. And these are specifically towards treating a neurologic disease by administering dimethyl fumarate or monomethyl fumarate or a combinate at least partially structured to dimethyl fumarate or monomethyl fumarate.
Q. Thank you, Doctor.

Let's look at Column 3, lines 10 through 15.

What does this portion of the patent indicate are the neurological diseases to be treated and the methods we just discussed?

A. The specification states "In some embodiments the neurologic disease is a degenerative disease such as ALS, Parkinson's disease, Alzheimer's disease, and Huntington's disease. In some embodiments, the disease is multiple sclerosis or another demyelinating neurologic disease."

And, of course, multiple sclerosis is by far the most common demyelinating neurologic disease.

Q. Thank you, Doctor.

Let's go to Column 8 of the patent, lines 34 through 54.

And is there more information provided here about Method 4?

A. Yes. Column 8 of the patent specification is a more detailed description of Method 4.

Q. Okay. And what does it tell us about the compounds that are associated with Method 4?

A. It specifically states that they include dimethyl fumarate and monomethyl fumarate in line 44 as well as in line 38.

Q. And looking at lines 45 through 47, what is this telling us about the neurological disease that is being treated with dimethyl fumarate or monomethyl fumarate pursuant to Method 4?

A. Again, the way I interpret this as a clinician, it states "to prevent or slow neurodegeneration; more specifically, demyelination, axonal loss, and neuronal death."

And, again, as discussed earlier, this is a theme that's repeated throughout as the hallmark findings that all students

of medicine would recognize are the hallmark findings that we see in multiple sclerosis.

Q. And, Doctor, how does -- this description of preventing neurodegeneration, demyelination, axonal loss, and/or neuronal death, how does that compare to the characteristics of multiple sclerosis that we saw at Column 1 of the '514 patent?

A. They are substantially the same.

Q. And let's go to Column 16, line 66. I want to extend that through column 17, line 45.

I'm sorry. I had a typo in my notes. I want to go to Column 16, line 66, through Column 17, and we can go to line 37 or so. Thank you.

So, Doctor, while we're putting it up on the screen, what is being described in this portion of the patent?

A. This simply describes that the compounds being used to treat neurologic disease will be studied in EAE, experimental autoimmune encephalomyelitis. EAE, as has been testified earlier, is the most common model we use for studying compounds for treating multiple sclerosis.

Q. And does the '514 patent include any examples that relate to the EAE mouse model that's described here as an animal model for multiple sclerosis?

A. Yes, it does.

Q. And which example is that?

A. Example 3.

Q. Okay. Why don't we go to Example 3. And that appears, for the record, at Column 20, beginning at line 63.

And can you explain to us what's being described in Example 3, Doctor?

A. Again, this is utilizing, again, a model for studying multiple sclerosis, EAE -- which, to my knowledge, is used for almost no other purpose -- for studying the compounds at interest here, such as dimethyl fumarate or monomethyl fumarate.

And so these are the last -- Example 3 are the last substantive paragraphs of the specifications. And so, as we've discussed, the first several substantive paragraphs of the specification all refer to describing multiple sclerosis, what is the disease, how it's characterized, its epidemiology, the pathological findings that we see in the disease.

And the patent ends with a description of the most common animal model of MS, EAE. So, really, to me, reading this, I see this as a patent which, from beginning to end, is a description of the treatment of multiple sclerosis.

Q. Thank you, Doctor.

Let's turn to the second element of the claimed invention that you identified earlier, the use of DMF and/or MMF. Let's go back to the methods we looked at earlier, at Column 3. And let's look at lines 1 through 4. Let's focus on Method 4 for now.

And what does this indicate are the compounds of interest for Method 4?

A. At least one compound that is partially structurally similar to dimethyl fumarate or monomethyl fumarate.

Q. Okay. Doctor, in your opinion, does the use of the language "partially structurally similar" indicate to you it is not directed to dimethyl fumarate or monomethyl fumarate?

A. No, it does not.

Q. Okay. And let's look at Column 4, lines 29 through 32.

What does this portion of the patent tell you about what compounds are the subject of Method 4?

A. Specifically, a fumaric acid derivative, e.g., DMF, dimethyl fumarate, or MMF, monomethyl fumarate. So this, to me, teaches me, in the longer description, that Method 4 includes -- the partially structurally similar includes DMF and MMF, which are obviously more than partially structurally similar but are identical to DMF and MMF.

Q. Thank you, Doctor.

Let's go to the additional discussion of Method 4 that appears at Column 8 of the patent, lines 35 through 50. And what is this portion of the patent telling you about the compounds that are the subject of Method 4?

A. We learn in line 38, again, it states "partially structurally similar to DMF or MMF." Skipping down to line 44, it states "a fumaric acid derivative, e.g., DMF or MMF,"

clearly teaching me that DMF and MMF are compounds that are being taught.

Q. Okay. And do any of the patent examples indicate in any way that DMF or MMF are compounds of interest to the claimed invention?

A. Yes. All three of them do.

Q. Let's look at the examples. Let's go first to Example 1. And that appears at Column 19, beginning about line 66.

THE COURT: May I interject for just a moment?

Could we send a message to Sheree to let her know it's approaching maximal heat in here. We went from arctic to desert, and we need to just get somewhere in the middle.

MR. BROWNING: Much appreciated, Your Honor.

BY MR. BROWNING:

Q. Doctor, picking up again, we're looking at Example 1. What --

THE COURT: Which column are you in?

MR. BROWNING: Thank you, Your Honor. It's Column 19, beginning at line 65 or so at the bottom of the page.

THE COURT: Thank you.

MR. BROWNING: You're welcome.

BY MR. BROWNING:

Q. And what does this portion of the patent indicate about Example 1 and what compounds are being studied?

A. In Example 1, dimethyl fumarate and monomethyl fumarate are being studied.
Q. Okay. And are any other compounds being studied in Example 1?
A. No.
Q. Let's look at Example 2. That's at Column 20, and it begins about line 19.
And looking a few lines down, what is the compound being studied in Example 2?
A. Dimethyl fumarate.
Q. Is any other compound studied in Example 2?
A. No.
Q. Let's go to Example 3. That's the mouse study that we discussed earlier. And Example 3, for the record, begins at Column 20 at about line 64.
And what compounds are being studied in Example 3? For the record, it appears in Column 21, line 4.
A. Dimethyl fumarate and monomethyl fumarate.
Q. Are any other compounds studied in Example 3?
A. No, they're not.
Q. Thank you, Doctor.
Let's now turn to the third element that you described. And that was use of a dosage of 480 milligrams per day, correct?
A. Yes.

Q. Okay. Let's go back to Column 4 of the patent. I want to focus you on lines 29 through 33.

Yes.

And do you see here it says that "In some embodiments, Method 4 comprises administering to the mammal a therapeutically effective amount of at least one neuroprotective compound"? And it gives several examples, including DMF or MMF, correct?

A. Yes.

Q. All right. Doctor, does the patent provide a definition of a therapeutically effective amount?

A. Yes. In Column 5, line 47, the terms -- I'm sorry -- line 53, "The terms 'therapeutically effective dose' and 'therapeutically effective amount' refer to that amount of a compound which results in at least one of prevention or delay of onset or amelioration of symptoms of a neurologic disorder in a subject in need of the desired biological outcome, such as reduced neuroregeneration (e.g., demyelination, axonal loss, and neuronal death) or reduced inflammation of cells of the central nervous system."

Again, the theme that we've repeated several times, and it's repeated throughout the specification.

Q. Thank you, Doctor.

And to be clear, that language, "demyelination, axonal loss, neuronal death," that's the same language we've seen

associated with multiple sclerosis as characteristics of the disease, correct?

A. That's correct.

Q. And that, among other places, appeared at Column 1?

A. Correct.

Q. All right. Thank you, Doctor.

And let's now go to Column 18. And let's look at lines 52 through 64.

And, Doctor, let me just first ask you, does this provide information about dosages of DMF or MMF to be used when practicing the claimed invention?

A. Yes, it does.

Q. Okay. And let's focus down on the -- about line 58.

I'm sorry. You know what? I want to go up a little bit. I want to go to line 54, and let's highlight from there down.

I'm sorry. I want to highlight down from the effective doses, down the next few lines.

Well, anyway, while we're highlighting, we can talk about it.

So do you see here the patent reads that "Effective doses will also vary, as recognized by those skilled in the art, depending on route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments, including use of other therapeutic agents."

A. Yes, I see that.

Q. Okay. And then it goes on, saying "For example, an effective dose of DMF or MMF" -- correcting the typo -- "to be administered to the subject orally," and let's pause there.

Has this portion of the patent now defined the route of administration that applies to the next dosages listed?

A. Yes. It specifically states this would be an effective dose given orally.

Q. Okay. And there was discussion during Dr. Greenberg's testimony that one of skill in the art would think the dosages would vary according to the patient's weight.

Do you recall that testimony?

A. I do recall that.

Q. Okay. And is -- the portion of the patent that we're highlighting and discussing now, does it say anything about varying the dose according to the patient's weight?

A. No.

Q. And let's go forward. There was also excipient usage, but we'll get back to that.

And proceeding on for administering DMF or MMF to a subject orally, what does it teach us are the doses of interest?

A. The patent begins with a very large range and lists a sequential narrower and narrower nesting ranges, calling one to 480 to 720, 720 being the known effective dose, 480 to 720 being the most narrow range listed in the patent specification,

hence drawing me to that specifically, the 480 dose.
Q. You indicated that 720 milligrams per day of DMF was a known effective dose?
A. Yes, as we reviewed in the O'Neill Biogen Phase 2 study presented by Dr. Kappos. In that study, the Phase 2 study of dimethyl fumarate, 720 was a known effective dose for treating multiple sclerosis.
Q. And I'm not exactly sure how it came out in the end, but I believe that Dr. Greenberg did testify that, within this section of dosing that's specifically directed to dosing DMF or MMF orally, that the dosage range of 480 to 720 milligrams per day is the narrowest range disclosed.

Assuming I've characterized his testimony correctly, would you agree with that?
A. I would.
Q. And, Doctor, let's go to the next page of the patent. And I want to direct you to Column 19, beginning about line 4 and extending all the way down to line 27.

And while we're highlighting that, I want to ask you, what's being described in this section of the patent?
A. In this section of the patent is the description of how to make the dose forms. Again, the different elements of treating MS with dimethyl fumarate or monomethyl fumarate, a dose of 480 milligrams per day, this section of the specification specifically describes how to make those dose forms. In the

final line of this paragraph, dimethyl fumarate and/or monomethyl fumarate are given in U.S. Patent 6,509,376, and 6,436,992.

So, as a physician, I would know which drug -- what illness I'm trying to treat, multiple sclerosis; what drug to use, DMF or MMF or a combination; what dose, 480. And, again, this section of the specification teaches me how to make those dose forms.

Q. And you'll recall, Doctor, there was some discussion of excipient usage. Does this section of the patent give you information about what excipients may be used and dosage forms?

A. It does.

Q. And let's just -- you pointed to two patents that are described here. And it says that "formulations containing DMF and/or MMF are given in, for example," and then it identifies two patents, the first being what we call the '376 patent, correct?

A. Yes.

Q. And you reviewed that patent in forming your opinions in this case?

A. I have.

Q. Okay. And let's just go quickly to DTX 1000. Is this the '376 patent, Doctor?

A. Yes.

Q. And let's just go quickly to Example 1, which appears at

Column 6. And what's being described in Example 1?
A. The preparation of enteric-coated microtablets in capsules of dimethyl fumarate.
Q. Okay. And you discussed earlier the formulation that was used in Biogen's Phase 2 studies as reported in the slides Kappos -- slides presented by Dr. Kappos. How does this formulation compare for that description of the formulation?
A. This formulation is identical to that described in Biogen's Phase 2 study presented by Professor Kappos.
Q. And was that the formulation that produced the result -- effective result in treating multiple sclerosis patients at a dosage of 720 milligrams per day of dimethyl fumarate?
A. Yes.
Q. Okay. Thank you, Doctor.
Have you prepared some -- we've worked together. Have you prepared some demonstratives that summarize your opinions concerning the written description support for the elements of the claimed invention?
A. I have.
Q. Okay. And if we can go back to the demonstratives.
And, for the record, we're beginning at PDX 3-14. And could you briefly go through these demonstratives and summarize your opinions concerning the written description support for the elements of the claimed invention.
A. Yes.

So, once again, the three elements of the claims are treating multiple sclerosis with dimethyl fumarate or monomethyl fumarate, a dose of 480 milligrams per day.

The written description in support for multiple sclerosis is -- from the very beginning of the subset of paragraphs of the patent specifications, as highlighted here in green, "treating neurological diseases including demyelinating neurological diseases, such as, e.g., MS," which, of course, we know is the most common demyelinating disease.

Q. And let's go forward to the next demonstrative. And that's PDX 3-15. And what's being described here, Doctor?

A. The different methods.

Again, as we discussed, Methods 1, 2, and 3 are methods of screening compounds for use. And Methods 4 and 5 are simply treatment -- methods of treatment of a neurologic disease such as multiple sclerosis with DMF or MMF. And, really, the different claims all -- the different elements all run through Method 4 here.

Q. Thank you, Doctor.

Let's go forward to the next demonstrative, PDX 3-16.

And what are you describing here?

A. Again, here, this is where there's excellent written description support for the use of dimethyl fumarate or monomethyl fumarate.

In Column 3, line 1 through 5, methods using dimethyl

fumarate or monomethyl fumarate. In Column 4, line 29 through 33, Method 4, e.g., DMF or MMF. And, again, in the column on the right on the demonstrative, the longer description of Method 4, one compound at least partially structurally similar to DMF or MMF. Again, the next paragraph, e.g., DMF or MMF.

In some embodiments of Method 4, a method of slowing or preventing neurodegeneration, more specifically demyelination, axonal loss, and neuronal death, hallmark findings we see in multiple sclerosis.

Q. Let's go forward to PDX 3-17. I think this is the last slide in the sequence. What is being described here?

A. Again, the final element is the 480 milligrams per day, and I've highlighted this aspect in yellow. In the red box, in the lower half of the demonstrative, progressively narrowing ranges, nesting ranges, leading one to the most narrow range, 480 to 720, 720 and anchoring to a known effective dose of 720, to 480, 480 being the lower end of the range, teaching me that 480 would be an effective dose for oral administration of dimethyl fumarate or monomethyl fumarate to someone with multiple sclerosis.

Q. Thank you very much, Doctor.

Let's go to -- back to the '514 patent. I want to look at the first page. And I want to look at the left-hand column, and I want to look at the section about midway through, "Related U.S. Application Data." If we could blow that up.

Doctor, do you understand that this portion of the patent identifies the priority filings associated with the '514 patent?

A. I do understand that.

Q. And are there two filings identified here?

A. Yes.

Q. And what are they?

A. The provisional application, the '921, filed February 8th, 2007; and the PCT application, February 7th, 2008.

Q. Thank you, Doctor.

And have you reviewed both of those documents in forming your opinions in this case?

A. I have.

Q. Let's turn first to JTX 2182. I'll ask you, Doctor, is this a provisional document dated February 7, 2007?

A. February 8th, 2007.

Q. Thank you, Doctor. Keeping me honest.

And did you review this document in forming your opinions in this case?

A. I did.

Q. And were there any substantive differences between the disclosure of the JTX 2182, the provisional application, that impact your written description opinion -- let me ask that again.

Are there any substantive differences between the

disclosure of the provisional application and the '514 patent specification?

A. No.

Q. And let's move forward to PTX 401.

And do you recognize this document?

A. I do.

Q. And is this the other priority document we just looked at on the face of the patent?

A. Yes.

Q. Okay. And you reviewed this document in forming your opinions?

A. I have.

Q. And are there any substantive differences between the disclosure of this document and the disclosure of the '514 patent specification?

A. No.

MR. BROWNING: Thank you very much, Doctor. I don't have any further questions for you at this time.

THE WITNESS: Thank you.

THE COURT: Thank you.

Cross-examination.

MR. ANSTAETT: Thank you, Your Honor. We have some binders to pass out, if that would be all right.

THE COURT: Thank you.

MR. ANSTAETT: Your Honor, I think we have everything

distributed, if I may proceed.

THE COURT: You may proceed.

CROSS-EXAMINATION

BY MR. ANSTAETT:

Q. Good afternoon, Dr. Wynn. How are you?

A. Very good. Thank you.

Q. Good. Let me try to orient you to the materials you have in front of you that you've just been handed.

You have a cross-examination binder, I believe, up there. Do you see that?

A. I do.

Q. Okay. And we've given you -- we've given you copies of your rebuttal expert report in this case and your various deposition transcripts. You were deposed in this proceeding and in a related IPR proceeding.

Do I recall that correctly?

A. Yes.

Q. And you were also deposed on behalf of Biogen in a case in Delaware, correct?

A. Yes.

Q. And you have that deposition transcript in your binder as well.

And I understand that you provided testimony on the issue of written description in the '514 patent on behalf of Biogen at trial in Delaware in December of 2019. Is that right?

A. That's correct.
Q. And we've given you a copy of your Delaware trial testimony as well.
Dr. Wynn, the task you were given in this case and in Delaware was to look at the claims of the '514 patent and assess whether there was written description support for them in the specification; is that right?
A. Yes.
Q. And is it fair to say you read the '514 patent specification very carefully and that you're quite familiar with it?
A. Yes.
Q. And that would go for the '921 provisional application as well that you just spoke about with your counsel?
A. Yes.
Q. Now, I understand you're not a lawyer, but I also know from your expert report that you got some instruction on the law to help you in forming your opinions in this case.
Is that right?
A. That's correct.
Q. And you know, therefore, that the question of written description is evaluated from the perspective of a person of ordinary skill in the art; is that right?
A. Yes.
Q. So reading a patent specification, a skilled artisan kind

of brings with them their education, their training, and the knowledge of the prior art; is that right?

A. That's fair.

Q. So -- and I don't think we'll have any disagreement on this because I believe you testified to it on direct, but skilled artisans, at the priority date of the '514 patent in February 2007, would have been aware of the Kappos Phase 2 trial that tested 120 milligrams, 360 milligrams, and 720 milligrams per day of DMF to treat MS; is that right?

A. I am. That's true.

Q. And the results of the Kappos Phase 2 trial were reported in 2006; is that right?

A. Yes.

Q. And, in your opinion, skilled artisans would have understood the Phase 2 trial as showing that only the 720-milligram-per-day dose of DMF was efficacious in treating MS; is that right?

A. Of the three active doses tested, only the 720-milligram dose was effective.

Q. Okay. And it wasn't until much later, in 2011, that Biogen reported the results of its larger Phase 3 define and confirm trials in which the 480-milligram dose of DMF showed efficacy in treating MS; is that right?

A. That's correct.

Q. And it's also your opinion, is it not, Dr. Wynn, that one

of ordinary skill would not have expected and could not have predicted the Phase 3 results based on the Phase 2 results?
A. It's my opinion that, based upon the Phase 2 results, the magnitude of treatment effect that was seen in Phase 3 could not have been predicted.
Q. You had a different opinion than that didn't you, Dr. Wynn? Not just the magnitude but the fact that the 480-milligram dose showed efficacy at all in the Phase 3 trial. Isn't that true?
A. If you'd like to refer me to a specific area, I'd be happy to look at that with you.
Q. Let's do that. It was your opinion that a person of ordinary skill in the art would not have expected 480 milligrams per day to be similarly efficacious to 720 milligrams per day based on the state of the art, right?
A. Yes.
Q. And, indeed, in your opinion, in view of the state of the art at the priority date, the fact that the 480-milligram-per-day dose of DMF even exhibited statistically significant efficacy in the Phase 3 studies was especially surprising, right?
A. I mean, prior to the reading the '514 patent, I would not think to even study a 480-milligram dose. After reading the patent, I would have learned that 480-milligram was an effective dose for treating multiple sclerosis.

Q. So let me ask my question again, Dr. Wynn.

In your opinion, in view of the state of the art at the priority date, the fact that the 480-milligram-per-day dose of DMF even exhibited statistically significant efficacy in the Phase 3 studies was especially surprising, right?

A. I think that it was quite surprising. The magnitude of this effect was surprising to me.

Q. Dr. Wynn, I think this is an important issue. I'm not talking about the magnitude of the effect. Okay? Your opinion that you offered in this case was the fact that it exhibited statistically significant efficacy at all was especially surprising, correct?

A. On clinical end points, that's correct.

Q. Thank you, Dr. Wynn.

And, in your opinion, based on the Phase 2 trial results, one skilled in the art would have had no reason to select a dose of 480 milligrams per day of DMF for investigation, correct?

A. Prior to reading the '514 patent, that would be my impression.

Q. Right. Based on the Phase 2 results, no reason for a skilled artisan to look at 480, right?

A. Not from my perspective.

Q. Okay. Now, as part of your work in this case -- and we've heard about this today -- you also reviewed a declaration

submitted by Biogen's Katherine T. Dawson to the United States Patent and Trademark Office in conjunction with the prosecution of the '514 patent, correct?

A. Yes.

Q. And let's look at JTX 2088 in your cross-examination binder, please.

A. The declaration of Dr. Dawson?

Q. Yes, sir. Do you have that?

A. I do.

Q. Okay. And this is the Dawson declaration that you reviewed in forming your opinions in this case, correct?

A. Yes.

Q. And I'm looking at page 19 of 68. I think those numbers may be in the bottom left-hand corner.

A. Page 9 of 68?

Q. 19 of 68, and it's paragraph 13.

Are you there?

A. Page 19, which paragraph?

Q. Paragraph 13.

A. Okay.

Q. All right. And in her declaration Dr. Dawson states, "As discussed above the Phase 2 clinical trial results demonstrated that 720 milligrams a day of DMF was efficacious in treating MS while 120 milligrams per day and 360 milligrams per day DMF dosing regimens were statistically indistinct from placebo.

Additionally, the Phase 3-defined study results demonstrated that 480 milligrams per day of DMF was efficacious in treating MS."

Do you see that?

A. I see that.

Q. And you agree with that, right?

A. Yes.

Q. And then she goes on in paragraph 14, "The positive and clinically meaningful results obtained with the 480-milligram-per-day dose of DMF were unexpected to me given, one, the Phase 2 clinical trial indicated that both the 120 milligrams a day and 360 milligram per day doses of BG-12 were not efficacious; and, two, there was no apparent linear dose response," correct?

A. That's what it states, yes.

Q. What's what Dr. Dawson told the U.S. Patent and Trademark Office, right?

A. Yes.

Q. And you agree with that, right?

A. I agree that's what her declaration states.

Q. You agree with her opinion, don't you?

A. Yes.

Q. So, in your opinion, that's kind of the baseline view of the prior art that the skilled artisan brings to reading the '514 patent specification. Is that fair to say?

A. It's fair to say that, prior to reading the '514 patent, that one would know one effective dose, 720 milligrams per day, to treat multiple sclerosis.
Q. Correct. And there was no reason a skilled artisan would select a dose of 480 milligrams a day of DMF for investigation into MS, right?
A. Prior to reading the patent, no. After reading the patent, yes.
Q. We'll get to that.
Okay. You talked with your counsel about the 921 provisional application.
Do you recall that?
A. I do.
Q. So let's look at JTX 2188 in your cross binder, please.
A. Yes.
Q. And just to lay the foundation here, you recognize this -- I want you to look at the second page of the document, sir. And you recognize this as the provisional patent application filed on February 8th, 2007, to which the '514 patent claims priority; is that right?
A. That's correct.
Q. Okay. And I'll call this the '921 provisional application. Okay?
A. Yes.
Q. All right. You discussed Example 3 in the '514 patent on

your direct testimony.

Do you recall that?

A. I do.

Q. Do you know if Example 3 was in the '921 provisional application?

A. There's description of EA model in the provisional but not the -- for example, pictures of NRF activation in the spinal cords of the mice or of the other graph, the second photograph.

Q. I'm sorry. I didn't mean to interrupt you, sir.

It talked about EAE, but Example 3 was not in the provisional; is that right?

A. I think EAE is described in the provisional.

Q. My question is about Example 3, sir.

A. The Example 3 in the '514 patent is the EA model. EAE is referenced in the provisional. However, the example is not as described in the provisional as it is in the '514 patent.

Q. Okay. So why don't you turn to page 4 of 48 in the provisional, and let me know when you're there.

A. I am.

Q. And, as filed, the patent application was titled "NRF2 Screening Assays and Related Methods and Compositions," correct?

A. Yes, I see that.

Q. And, now, you're not an expert in NRF2 activation; is that right?

A. Not specifically.
Q. And you're not an expert on using NRF2 activation to screen for compounds in drug discovery; is that right?
A. Correct. My basic science years of my career are past.
Q. And before the use of DMF to treat MS became known, the NRF2 pathway was not on your radar screen, right?
A. That's correct.
Q. And at least in isolation, if an individual drug simply had an effect on the NRF2 pathway, that would not tell you, in and of itself, whether or not that would be a drug necessarily to administer to a person with multiple sclerosis, correct?
A. If what you mean in isolation would be, no. We know the NRF2 pathway is a pathway that's activated in reaction to injury, and one of the problems, as described in the specification in the provisional and the '514 patent, is that we have drugs at the time of the application, 2007, that decrease inflammation but none that really reverse the damage that occur in MS, not that really work on the degenerative aspects of MS, hence, of course, listing other than diseases than MS by themselves.
Q. Are you done?
A. Yes.
Q. You would agree, though, in isolation, simply a drug that has an effect on the NRF2 pathway, that wouldn't tell you, in and of itself, whether that drug could be used to treat MS? We

agree on that at least?
A. Well, it's true that an effective NRF2 would not be a reason to study a drug by itself. To the extent that we can activate NRF2 pathway, as has been shown for DMF and MMF in the Examples 1 through 3 of the '514 patent and the other example -- the other examples simply listed in the provisional, if we can activate a reparative pathway, that would be beneficial for treating a degenerative disease such as multiple sclerosis.
Q. I think I got the answer to my question.
If you'll turn to page 31 of 48 in the '921 provisional application, sir.
A. Yes.
Q. Do you see there's a heading there that says "Neurological Diseases"?
A. I do.
Q. All right. And right underneath that, paragraph 104 mentions MS, but it first says "A neurological disease in Methods 1 through 5 above can be a neurodegenerative disease, such as, for example, ALS, Parkinson's disease, Alzheimer's disease, and Huntington's disease," correct?
A. Yes.
Q. So it's not limited to MS; is that right?
A. Correct.
Q. Okay. And then in paragraphs 106 and 107, we get a very

lengthy list of what are described as neurological diseases suitable for the methods of the invention, correct?

A. It does state that, yes.

Q. And that's how the patentee chose to define neurological diseases in the context of this patent; is that right?

A. Well, many diseases are listed in this patent. The patent from beginning, the first substantive paragraphs of the patent, are all in the description of multiple sclerosis, and the '514 patent, of course, ends in studying EAE, the main animal model for studying MS. I can only conclude the '514 patent is about treating MS but not necessarily exclusively multiple sclerosis.

Q. There's a -- paragraphs 106 and 107 set out how the inventors have described neurological diseases in the '514 patent.

Is it that fair?

A. Yes.

Q. Turn to page 34 of 48 of the provisional, please.

A. Yes.

Q. Do you see there's a heading there that says "Dosages and Formulations"?

A. I do.

Q. And that's the dosing section of the patent application, right? Starting at paragraph 112?

A. Yes.

Q. And it runs through paragraph 121, and then the examples

start, correct?
A. Yes.
Q. All right. And within that dosing and formulation section is paragraph 116, which is the one place in the specification that you point to for support for the specific 480-milligram daily dose of DMF in MS, correct?
A. That's correct.
Q. And in this entire dosing and formulation section in the specification, multiple sclerosis is never mentioned, correct?
A. Yes. While multiple sclerosis is not mentioned in paragraph 116, again, this dosing section, the section that's to teach me how much to give, is with a patent which describes MS literally over 30 times.
Q. And I'm just -- I just want to be clear. You referenced paragraph 116. I'm talking about that entire dosing and formulation section that runs from paragraphs 112 to 121, MS isn't mentioned anywhere in there, right?
A. Not any more than what I described.
Q. And it is true -- or that is true, I should say, not just in the '921 provisional application but also in the '514 patent specification itself, correct?
A. Yes.
Q. Okay. Let's look at JTX 2000, please, which is the '514 patent.
A. Yes.

Q. Okay. You would agree with me, Dr. Wynn, that there's no experimental data in the patent specification demonstrating the therapeutic efficacy of a 480-milligram daily dose of DMF to treat MS, correct?

A. There's no dose -- there's no data regarding treatment of humans in the '514 patent.

Q. Okay. And this dosing section that we just talked about when we looked at the '921 -- actually, let me take a step back.

If you'll turn to Column 17, starting at line 59, through Column 18 at line 2. And if you'll just let me know when you're there.

A. I'm sorry. Column 17, did you say?

Q. Yes, sir. Column 17, line 59, through Column 18, line 2.

A. Yes.

Q. And this is the beginning of the dosing section we just talked about in the provisional, right?

A. Correct.

Q. Okay. And at the beginning of this paragraph it says "Preliminary doses, for example, is determined in animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices."

Do you see that?

A. I see that.

Q. And that's not limited to MS, correct? It could cover any

of the neurological diseases in the specification?

A. Fair enough.

Q. Okay. And then let's look at the next paragraph, Column 18, starts at line 3. And let me know when you're there.

A. I am.

Q. It says "The therapeutically effective doses can be estimated initially from cell culture assays."

Do you see that?

A. I do.

Q. And that's another general way of coming up with a dose of a drug, and it's not limited to MS, right?

A. Yes. Clearly, one would start with simple experiments, in vitro experiments, like cell culture, and only after that scaling it up to an animal model study, such as EAE that, of course, the most common in vivo model for studying multiple sclerosis.

Q. But here in column -- we agree Column 18, line 3, that paragraph covers all the various diseases that were set out for treatment, right?

A. Correct.

Q. And if you look at the next paragraph in Column 18, lines 14 to 21. Do you see that?

A. I do.

Q. And it says "The data obtained from the in vitro assays or

animal studies can be used in formulating a range of dosages for use in humans," correct?

A. Yes.

Q. That's not specific to MS either, right?

A. That would be correct.

Q. It's applicable to all the diseases that are set forth in the patent, correct?

A. Yes.

Q. All right. Now, in the paragraph there's Table 2.

Do you see that?

A. I do.

Q. And then in the paragraph immediately below that in Column 18, it says -- and I'm reading about halfway down -- "Generally, a therapeutically effective amount may vary with the subject's age, condition, and sex, as well as the severity of the medical condition in the subject. Examples of pharmaceutically acceptable doses for compounds described herein are from 1 microgram per kilogram to 25 milligrams per kilogram depending on the compounds, the severity of the symptoms, and the progression of the disease."

Do you see that?

A. I see that.

Q. Now, you wouldn't regard that passage to be referring to the treatment of MS with DMF, correct?

A. I don't know that it would not have to do with multiple

sclerosis, but it would not be exclusively for multiple sclerosis.

Q. Well, I'm not just asking about multiple sclerosis. You wouldn't regard that passage about being -- about the use of DMF to treat MS, right?

A. I'm sorry. Could you repeat that?

Q. Sure. You wouldn't regard that passage that I just read to be referring to the treatment of multiple sclerosis with DMF, right?

A. I would say that these are steps one takes in developing a compound and a dose for treating multiple sclerosis.

Q. We don't vary the amount of DMF that you administer to a multiple sclerosis patient based on their age, their condition, or their gender, do you?

A. No.

Q. Okay. And with DMF and MS, you can't individualize a dose for a given patient like you can for pain or hypertension or psoriasis, for example, because, in MS, if you wait until you have symptoms, you already can have damage to the brain.

Isn't that right?

A. That would be correct.

Q. Okay. All right. Now, I want to take a look at your direct examination slides. And I don't know if we can pull those up. If not -- they're in your -- did we lose our monitor?

MS. BLOODWORTH: We lost power.

THE COURT: I really hate to interrupt your cross-examination; but, given the fact of the loss of power, we'll see if we can remedy that and we'll take -- I know we need to get through Dr. Wynn. What else do we have today? I want to know whether one hour or one, fifteen, two hours. What do you need?

MR. ANSTAETT: Your Honor, my understanding is, once I'm done with my cross, and of course if Mr. Browning has any redirect, that will be it for today because we're still working out the deposition designations for Drs. O'Neill and Dawson.

THE COURT: Dr. Wynn, are you headed to a plane at a particular time?

THE WITNESS: I'm out of my hotel around 3:30.

THE COURT: You need to be out of here by 3:30?

THE WITNESS: I should probably be out of here by 3:00.

THE COURT: Okay. He's headed back to Pittsburgh?

MR. BROWNING: Yes, Your Honor.

THE COURT: Okay. So if we recess until 1:15 -- the reason I'm hesitating. I don't know if we've lost power, if we have to get somebody over here, or if it's a city-wide event based on snow. You know what I'm saying?

So we'll say 1:15, and I'll let you know at 1:15 if we need little bit more time. How's that?

Court stands in recess until 1:15.

Dr. Wynn, you remain on cross-examination. And even though you're an expert, at least in my court, that means you can't talk to anybody from the Biogen team about your testimony during your recess. Okay?

THE WITNESS: Thank you very much.

THE COURT: Thank you.

(Lunch recess taken, 12:15 to 1:15.)

THE COURT: You may continue.

MR. ANSTAETT: Thank you, Your Honor.

BY MR. ANSTAETT:

Q. Welcome back, Dr. Wynn.

A. Thank you.

Q. I will try to move this along so we can get you on your plane.

When we broke, we were about to look at your demonstrative exhibits that you used in your direct examination.

And if we could please see Slide PDX 3-7.

All right, Dr. Wynn. And this shows Claim 15 of the '514 patent. This was kind of the representative claim you selected to talk about the elements of the claims, the main elements of the claims; is that right?

A. That's correct.

Q. Okay. And it looks like you've got some -- it's a little bit harder to see on the screens here, but certainly in my

copy, hard copy, it looks like you've got some color coding on that slide; is that right?

A. That's correct, sir.

Q. And the color for your support for the 480-milligram dose is orange; is that right?

It doesn't look very orange up there, but at least on the hard copy on mine, it was orange.

Does that sound right?

A. The last several words, correct.

Q. Okay. And as I looked through your direct examination slide, the only other slide where we see the orange color is on Slide PDX 3-17. Is that right?

A. I don't have my demonstratives here. That's the one section of the specification that refers specifically to the dose.

Q. The 480-milligram dose. And if you want to look at your demonstratives, they are in your cross binder. But I don't think we need to do that.

Let's put up PDX 3-17 on the screen, please.

This shows the '514 patent at Column 18, lines 52 to 64, correct? That's where the orange is?

A. Yes.

Q. Okay. And this is the only place in the entire patent specification where you find support for a specific 480-milligram dose of DMF, correct?

A. Well, this is the section of the patent that lists 480.
Q. It's the only place in the entire patent specification that lists 480. Can we agree on that?
A. This is the -- while this is the only section of the patent that specifically lists 480, an effective dose is -- for treating MS is listed in different sections of the patent, as we discussed. This is the one section that lists a specific dose of 480 milligrams per day.
Q. Well, you -- I believe you pointed to the definition of therapeutically effective dose, but that didn't have any particular dose in it, right?
A. That's correct.
Q. Okay. 480, you're familiar with the specification. Column 18, this is the only place it is, right?
A. That's correct.
Q. Okay. And multiple sclerosis is not mentioned in this paragraph, correct?
A. That's correct. While multiple sclerosis is not listed in this paragraph, multiple sclerosis of course is listed from the first substantive paragraphs of the specification to the end of it and is listed, in fact, over 30 times throughout the specifications.

This is the section that leads me -- teaches me what dose to use in treating somebody with multiple sclerosis.

Q. So MS is mentioned 30 times, right?

A. Yes.
Q. And 480 is mentioned once?
A. That's correct.
Q. Okay. And, again, multiple sclerosis that we agree -- and I think we went through the whole dosage and formulation section -- not mentioned in that entire section, including this section, right?
A. Right. This section simply tells me which dose to use to treat MS with DMF or MMF.
Q. All right. And in this paragraph, there's no rationale provided for the selection of a 480-milligram-per-day dose as being a superior dose for the treatment of MS, right?
A. A skilled artisan, in reading this, as you discussed with me earlier, would be aware of the O'Neill Biogen Phase 2 study presented by Professor Kappos that 720 was an effective dose.

This linked dose of unknown efficacy, 480, in the lowest range of 480 to 720, as an effective dose, teaching me that 480 would work. Prior to reading the patent, I would have not thought of 480. After reading the patent, I'm taught 480 would be an effective dose for treating multiple sclerosis.

THE COURT: Doctor, I'm just going to say this.

On cross-examination, typically, as an expert, you've got some leeway, but you should answer the question and then rely on your attorney to bring up the points you're trying to make now on redirect so that we can move through this.

Because your attorney is going to do that anyway. So if you do want to make that plain, it's probably smarter to move it along. I know he's going to ask you to clarify those points, but if you do that when you're supposed to be answering yes or no and you're not asked to explain, that's really not part of the rules on cross-examination.

THE WITNESS: Thank you, Your Honor.

THE COURT: You're welcome.

BY MR. ANSTAETT:

Q. So, Dr. Wynn, in this paragraph, there's no rationale provided for the selection of a 480-milligram-per-day dose as being a superior dose for the treatment of MS, correct?

A. Correct.

Q. Okay. And there are four dose ranges listed here; is that right?

A. Yes.

Q. All right. And when I say "listed here," I'm talking about Column 18, lines 58 to 62.

And, Dr. Wynn, reading this patent specification, in view of the prior art at the priority date, you would not have expected a dose range of 100 milligrams to 1,000 milligrams of DMF to be effective in treating MS; is that right?

A. That's correct.

Q. Okay. And that's the .1 gram to 1 gram per day, right? That's 100 milligrams to 1,000 milligrams?

A. Yes.
Q. Wouldn't expect it to be effective in MS?
A. Not all of those dosages.
Q. Right. And a skilled artisan, at the priority date, would have not expected a dose range of 100 to 1,000 milligrams to be effective for treating MS, right?
A. Correct.
Q. Okay. And reading this patent specification at the priority date in view of the prior art, you also would not have expected a dose range of 200 milligrams to 800 milligrams of DMF per day to be effective in treating MS, correct?
A. Correct. The only dose that I would know prior to reading the patent would be the dose of 720.
Q. Right. And so 200 milligrams to 800 milligrams, a skilled artisan, you would know 200 milligrams ineffective, right?
A. Correct.
Q. And reading the patent specification at the priority date in view of the prior art, you would not have expected a dose range of 240 milligrams to 720 milligrams of DMF per day to be effective in treating MS, correct?
A. I would not expect the lower estimate of the range to be effective, that's correct.
Q. 240 milligrams, wouldn't have any expectation that that would be effective, right?
A. That's correct.

Q. And a skilled artisan would have taken the same view, in your opinion, correct?
A. With that directive, yes.
Q. So you agree that, here in Column 18, we see set forth three ranges that include doses that skilled artisans at the priority date would regard as ineffective in treating MS, right?
A. Generally speaking, that's correct.
Q. Okay. Now, in one of these three ineffective dose ranges, a 240-milligram-a-day dose is linked to a 720-milligram dose, right?
A. Yes.
Q. But you don't think a skilled artisan reading the patent application would believe a 240-milligram dose would be effective to treat MS despite that linkage. Isn't that right?
A. That's correct.
Q. So you would not, and a skilled artisan would not, believe that the inventors possessed a 240-milligram-per-day dose of DMF to treat MS, correct?
A. Not to treat MS. And, of course, the paragraph mentions -- the specification of this other disease other than MS.
Q. Exactly. I think we can agree on this, Dr. Wynn.
The skilled artisan reading this section of the patent would look at those and say three of those four dose ranges

must be talking about some other neurological disease -- right? -- not MS?

A. I think that at the time prior to the patent, the only dose one would know is 720. Doses lower than 360 and below would be felt to be not effective.

Q. Right. So a skilled artisan reading that specification knows that three of the four dose ranges listed can't be talking about MS, right? Why would the inventors list ineffective doses in a range if this was about MS?

Can we agree on that?

A. While I would say that a dose of 360 and less would not be effective, I don't write patents; I read them. So I don't know how they write them.

Q. All right. But in any event, you're confident that a skilled artisan, at the priority date, looking at Column 18, when it says, quote, for example, an effective dose of DMF or MMF to be administered to a subject orally can be from about .1 grams to 1 gram per day, 200 milligrams to about 800 milligrams per day, e.g., from about 240 milligrams to 720 milligrams per day, unquote, the patent must be speaking about something other than effective doses in MS in that passage, right?

A. I would disagree.

Q. You would disagree?

A. So if we looked at the patent definition of therapeutically effective dose, therapeutically effective

amount is in Column 5 of the patent, lines 52 down, lower doses may have an effect on demyelination.

Nothing in the patent specification at any of the ranges states which dose would be the ideal dose or preferred dose. They all may have some effect on neurodegeneration, demyelination, axonal loss, nerve fiber loss, less lesions, but it doesn't say which is the preferred dose at any aspect of the specification.

Q. Your testimony, Dr. Wynn, now is that all four of those ranges, skilled artisans would look at those and think they were -- the three that we just went through were potentially effective doses in MS?

A. I don't think that one would choose a dose -- prior to reading the patent, I wouldn't choose a dose less than 720 to treat MS. Prior to reading the patent, I would think 480, by being the lowest aspect of the most narrow range, would be an effective dose to treat MS. But I don't know from reading this which would be the preferred dose to treat MS based upon the patent alone.

Q. So based upon reading the patent alone, you wouldn't know what the preferred dose was for treating MS? Is that what I just heard you say?

A. Which would be the most effective dose.

Q. Okay. You wouldn't know that?

A. Correct.

Q. Okay. Now we come to the dose range of 480 milligrams to 720 milligrams, correct?
A. Yes.
Q. All right. And so, according to you, we're shifting mid paragraph here to DMF for the use in multiple sclerosis, right?
A. And it states an effective dose of DMF or MMF, to be -- to be administered orally, would be that dose.
Q. Well, orally for what?
A. In the context of the patent, multiple sclerosis.
Q. Okay. Even though those three ranges that precede that one aren't for multiple sclerosis?
A. They would not be an ideal dose for treating multiple sclerosis based on the data that an artisan would know at the time of the filing of the patent.
Q. Based on the data the artisan would know at the time of the filing of the patent, all three of those ranges include doses which, according to you, they would know would be ineffective, right?
A. A dose of 360 or lower would not be felt to be a preferred dose for treating MS.
Q. Okay. So -- but we get to the fourth dose, and suddenly now we're talking about treating MS, right?
A. I don't know that the others were not for treating MS. And, again, from reading this, I don't know that 480 would be the preferred dose for treating MS either.

Q. And that's -- I think we agree on that. Reading this patent specification as a person of skill in the art, you wouldn't know that 480 milligrams would be a preferred dose for treating MS. I agreed with you on that, right?

We agree on that?

A. Okay.

Q. Okay. And, in fact, as discussed -- as we discussed earlier, efficacy at 480-milligram-daily dose would have come as a surprise to skilled artisans, right?

A. Prior to reading the patent, yes. After reading the patent, no.

Q. Well, I just thought you told me that you wouldn't have an expectation -- you wouldn't know, reading the patent, including the portion of it that you just pointed out here, skilled artisans wouldn't have -- wouldn't know if 480 milligrams was an effective dose?

A. I think that's not quite what I said. I think what I said was I wouldn't know from reading the specification what would be the most effective dose or best-tolerated dose, the preferred dose for treating MS.

Q. Okay. You would not know from reading the specification that 480 milligrams was a preferred dose for treating MS?

A. I wouldn't know it was the most effective of the doses. I wouldn't know -- we anchor 480 to -- inventors anchor 480 to a known effective dose of 720.

And so I'm directed to a lower range of the most narrow range in the nested ranges of doses in this patent. This patent teaches me to use 480. What would be the clinical response in using it in a trial, you know, would not be known at the time of reading the patent.

Q. Dr. Wynn, isn't it true that, if you had seen the '514 patent in 2007 at the priority date, you still wouldn't know whether the 480-milligram-daily dose of DMF was clinically effective in MS?

A. I think the patent teaches me that 480 milligram is an effective dose in treating MS.

Q. Dr. Wynn, I'm going to ask you one more time.

If you had seen the '514 patent in 2007 at the priority date, you still wouldn't know whether the 480-milligram-daily dose of DMF was clinically effective in MS.

Isn't that right?

A. I think the patent specifically states an effective dose of DMF or MMF administered orally is an effective dose in treating the disease.

Q. Dr. Wynn, could you look in your binder there at your Delaware trial transcript, please.

Let me know when you have that, and I'll direct you to a page.

A. Delaware trial testimony?

Q. The Delaware trial testimony, yes, sir.

A. I have that. Which page, sir?
Q. So 694.
All right, Doctor. I'm looking at the Delaware trial transcript at page 64, lines 13 to 18.
Do you see that?
A. I'm sorry. Page 694, did you say?
Q. 694, yes, sir.
A. Yes.
Q. And do you see you were asked a question there, "Actually, sir, if you had seen this patent in 2007, you wouldn't know about the 480 milligram dose, would you?"
And what was your answer?
A. I answered, "I wouldn't know if it was clinically effective."
Q. And then you were asked, "Because there's no data on it provided in the specification, right?"
And what did you answer?
A. "Anywhere that I'm aware of."
Q. All right. That was the testimony you gave in Delaware, correct, sir?
A. Yes.
Q. All right. Isn't it also true, Dr. Wynn, that you believed that the inventors had possession of the claimed invention because they had information on the 480-milligram dose that skilled artisans weren't privy to that is not

included in the patent specification?
A. I think it's fair that the inventors invented something and had insight in -- that 480 would be an effective dose. There are many things that may render a dose effective or ineffective clinically.
Q. But it was your belief that they were privy to information that they did not include in the specification of the '514 patent that led them to believe that the 480-milligram dose was effective, correct?
A. Yes. We know from subsequent testimony in the Delaware case and others that Dr. O'Neill had -- his idea all along was to treat MS with 480 milligrams a day of dimethyl fumarate.
Q. All right. And confidential information outside the patent specification is not sufficient to satisfy the written description requirement, right? The written description requirement is about disclosure?
A. That's correct.
Q. All right. And in your opinion, Dr. Wynn, the state of the art at the priority date actually taught away from a 480-milligram dose of DMF to treat MS; isn't that right?
A. Prior to reading the patent, I would have looked at a dose of the 720 or higher, given the relatively lackluster effect of the 720 in the Biogen O'Neill Phase 2 study as presented by Professor Kappos. After reading the patent, I would be directed towards 480 to 720, 480 being the lowest aspect of

that range.

Forgive me if I'm giving long answers, Your Honor.

Q. Are you done?

Okay. Well, I think we've covered what you would have thought when you read the patent specification. But I do agree with you, it was your opinion -- right? -- that skilled artisans, based on the prior art at the priority date would have been directed to higher doses than 720, not lower doses?

A. I would have thought that the 480 would have worked more like the 360-milligram dose than the 720-milligram dose.

Q. Okay. Just a couple more questions, Dr. Wynn.

You testified about Examples 1, 2, and 3 in the '514 patent, correct?

A. I believe so.

Q. All right. And you are aware, aren't you, that Dr. O'Neill has testified that he was not involved in Examples 1, 2, or 3 in the patent specification?

A. Yes.

MR. ANSTAETT: Thank you, Dr. Wynn. I have no further questions.

THE COURT: Redirect.

MR. BROWNING: May I proceed, Your Honor?

THE COURT: Yes. Certainly.

MR. BROWNING: Could we put back up PDX 3-17 of the opening of Dr. Wynn's slides.

REDIRECT EXAMINATION

BY MR. BROWNING:

Q. I want to ask you about your testimony about clinically effective, Doctor. Can you explain to us, what does it mean for a dose to be -- show efficacy at clinical end points?

A. So I'd like to see a person have less episodes of symptoms -- weakness, numbness, loss of bladder or bowel control, not loss of visual, less relapses -- and not progression of physical symptoms. That would be the clinical end point that all doctors use in treating individuals living with this horrible condition.

Q. Is that a standard typically associated with Phase 3 trials in drug development?

A. That's correct.

Q. Okay. And we talked earlier about the definition of therapeutic efficacy in the '514 patent. Do you recall that?

A. I do.

Q. Okay. And if you have the '514 patent, I know you know where it is. Go to Column 5.

A. Yes.

Q. What is the definition of therapeutic efficacy in the '514 patent?

A. On Column 5, line 52, the specification states "The terms 'therapeutically effective dose' and 'therapeutically effective amount' refer to that amount of a compound which results in at

least one of prevention or delay of onset or amelioration of symptoms of a neurological disorder in a subject or an attainment of a desired biological outcome such as reduced neurodegeneration, e.g., demyelination, axonal loss, and neuronal death, or reduced inflammation of the cells of the central nervous system."

Things actually we can see on MRI scan, for example.

Q. Okay. Is that different than the clinical end points or clinically effective that we just discussed?

A. Yes.

Q. Okay. Does this nevertheless provide a meaningful benefit for a patient?

MR. ANSTAETT: Objection. Leading.

THE COURT: Overruled.

BY MR. BROWNING:

Q. How does this impact a patient, this type of therapeutic efficacy?

A. Clearly, the fewer scars one has in the brain as seen in MRI scan, the better it is. People obviously, when I show them their MRI scan, what they're all hoping I'll say is "no new lesions."

Q. Thank you, Doctor.

Let's go to the demonstrative that I called up earlier. And, Doctor, let's look at the box, the red box.

Do you have an opinion as to what is the most preferred

range of the listed ranges in this box?
A. I do.
Q. And what is that?
A. 480 milligrams to about 720 milligrams per day.
Q. And did you explain that in your direct testimony?
A. I did.
Q. Okay. I don't think we need to belabor it.
I have no further questions for you, Doctor. Thank you for your time.
THE COURT: Thank you.
Anything further?
MR. ANSTAETT: No, Your Honor. Thank you.
THE COURT: Thank you, Dr. Wynn. You're finished, and you're excused as a witness and free to make your plane.
THE WITNESS: Thank you very much, ma'am.
THE COURT: You're welcome.
What do you want to do next?
MS. BLOODWORTH: So, Your Honor, I think we just have dep designations to play on Monday. We will have three witnesses. The parties are still working on Lansden's dep designations.
THE COURT: Okay. Dawson, O'Neill and --
MS. BLOODWORTH: Lansden.
THE COURT: Lansden. Okay. And is that it?
MS. BLOODWORTH: And then that will be it, yes, Your

Honor, but for closings.

MR. BROWNING: Yes, Your Honor, it's our understanding that that will be it.

THE COURT: Okay. Do you think closings will occur on Monday, or do you want to have a short day and do them on Tuesday morning? It's up to you.

Looking to the victims who will be doing closing argument.

MR. BROWNING: You're correct, Your Honor. The victim says Tuesday.

MS. BLOODWORTH: Your Honor, I think we'll probably take most of the day, maybe till about 3:00, 3:30, with the dep designations.

I know that Lansden is about an hour, and I would expect O'Neill and Dawson to at least be an hour and a half or so each.

THE COURT: Okay. Very well, then. Now, are you all going to be here this weekend, or do you have to fly out and return, because we could start out at 9:30 Monday morning if you think you can get the day in since it's a Monday, but I'm happy to start anytime.

MS. BLOODWORTH: We're here for the weekend, Your Honor.

THE COURT: Are you all as well?

MR. BROWNING: Yes, Your Honor.

THE COURT: So we'll do it at 9:00, then, begin at 9:00 on Monday morning. And then we'll go as long as we have to, and then we'll conclude on Tuesday morning.

And per side, are you looking for an hour, an hour and a half?

MR. ANSTAETT: Your Honor, for our part I think an hour will be sufficient.

MR. BROWNING: For us as well.

THE COURT: I think we have agreement there. One hour per side.

So what we'll do on Tuesday morning, unless I change my mind on Monday afternoon because you all want me to, but I think 10:00 to give you an opportunity to get up and ready yourself and get in here.

Will there be new exhibits or different exhibits for the closing argument -- I just want to know what to have with me -- referencing your demonstratives or anything that I should have up here while you're doing your closing?

MR. ANSTAETT: Speaking for myself, Your Honor, I think we'll have new closing demonstratives to provide to the Court. And I think, you know, in my view, that will be sufficient. If we have something from an exhibit that we want to show, we'll probably put it on a demonstrative.

MR. MONROE: Agreed.

THE COURT: Okay. Fine. Thank you very much.

Thank you all so much. I have learned a lot. I may want to take a few minutes at the conclusion on Monday to ask some questions of you all, and we'll move on from there.

The Court stands adjourned. Please have a pleasant weekend. If there's enough snow, there is skiing nearby.

(Proceedings adjourned at 1:44 p.m.)

CERTIFICATE

I, Cindy L. Knecht, Registered Professional Reporter and Official Reporter of the United States District Court for the Northern District of West Virginia, do hereby certify that the foregoing is a true and correct transcript of the proceedings had in the above-styled action on February 7, 2020, as reported by me in stenotypy.

I certify that the transcript fees and format comply with those prescribed by the Court and the Judicial Conference of the United States.

Given under my hand this 7th day of February 2020.

/s/Cindy L. Knecht

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Cindy L. Knecht, RMR/CRR
Official reporter, United States District Court for the Northern District of West Virginia